

**APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)**

1. * TYPE OF SUBMISSION		3. DATE RECEIVED BY STATE	State Application Identifier
<input type="checkbox"/> Pre-application <input type="checkbox"/> Application <input checked="" type="checkbox"/> Changed/Corrected Application			
2. DATE SUBMITTED	Applicant Identifier	4. a. Federal Identifier	
07/11/2013	PD/2013/01105	MH101637	
5. APPLICANT INFORMATION		* Organizational DUNS: 1672049940000	
* Legal Name: Research Foundation for Mental Hygiene, Inc.			
Department: 110 NYPI Translational Imaging		Division:	
* Street1: NYPI			
Street2: 1051 Riverside Dr			
* City: New York		County / Parish: New York	
* State: NY: New York		Province:	
* Country: USA: UNITED STATES		* ZIP / Postal Code: 10032	
Person to be contacted on matters involving this application			
Prefix: Ms.	* First Name: Janelle	Middle Name: Rene	
* Last Name: Greenhill		Suffix: MPH	
* Phone Number: 212-543-5801		Fax Number: 212-543-6062	
Email: nga@rf.cpmc.columbia.edu			
6. * EMPLOYER IDENTIFICATION (EIN) or (TIN): 1141410842A2			
7. * TYPE OF APPLICANT: M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)			
Other (Specify):			
Small Business Organization Type <input type="checkbox"/> Women Owned <input type="checkbox"/> Socially and Economically Disadvantaged			
8. * TYPE OF APPLICATION:		If Revision, mark appropriate box(es).	
<input type="checkbox"/> New <input checked="" type="checkbox"/> Resubmission <input type="checkbox"/> Renewal <input type="checkbox"/> Continuation <input type="checkbox"/> Revision		<input type="checkbox"/> A. Increase Award <input type="checkbox"/> B. Decrease Award <input type="checkbox"/> C. Increase Duration <input type="checkbox"/> D. Decrease Duration <input type="checkbox"/> E. Other (specify): _____	
* Is this application being submitted to other agencies? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> What other Agencies?			
9. * NAME OF FEDERAL AGENCY:		10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:	
National Institutes of Health		TITLE: _____	
11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:			
Neural mechanisms of sensory predictions in schizophrenia with hallucinations			
12. PROPOSED PROJECT:		* 13. CONGRESSIONAL DISTRICT OF APPLICANT	
* Start Date 04/01/2014	* Ending Date 03/31/2019	NY-013	
14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION			
Prefix: _____	* First Name: Guillermo	Middle Name: _____	
* Last Name: Horga		Suffix: _____	
Position/Title: Associate Research Scientist			
* Organization Name: Research Foundation for Mental Hygiene, Inc.			
Department: 110 NYPI Translational Imaging		Division:	
* Street1: NYPI			
Street2: 1051 Riverside Dr			
* City: New York		County / Parish: New York	
* State: NY: New York		Province:	
* Country: USA: UNITED STATES		* ZIP / Postal Code: 10032	
* Phone Number: 212-543-5805		Fax Number: _____	
* Email: horgag@nyspi.columbia.edu			

15. ESTIMATED PROJECT FUNDING		16. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?	
a. Total Federal Funds Requested	930,959.00	a. YES	<input type="checkbox"/> THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
b. Total Non-Federal Funds	0.00	DATE:	<input type="text"/>
c. Total Federal & Non-Federal Funds	930,959.00	b. NO	<input checked="" type="checkbox"/> PROGRAM IS NOT COVERED BY E.O. 12372; OR <input type="checkbox"/> PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW
d. Estimated Program Income	0.00		
17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)			
<input checked="" type="checkbox"/> * I agree <small>* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.</small>			
18. SFLLL or other Explanatory Documentation			
<input type="text"/>		<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>
		<input type="button" value="View Attachment"/>	
19. Authorized Representative			
Prefix: Ms.	* First Name: Janelle	Middle Name: Rene	
* Last Name: Greenhill		Suffix: MPH	
* Position/Title: Director of Administration			
* Organization: Research Foundation for Mental Hygiene, Inc.			
Department: 110 NYPI Facilities and Admini	Division: <input type="text"/>		
* Street1: NYPI			
Street2: 1051 Riverside Dr			
* City: New York	County / Parish: New York		
* State: NY: New York	Province: <input type="text"/>		
* Country: USA: UNITED STATES	* ZIP / Postal Code: 10032		
* Phone Number: 212-543-5801	Fax Number: 212-543-6062		
* Email: nga@rf.cpmc.columbia.edu			
* Signature of Authorized Representative		* Date Signed	
<input type="text"/> Ms. Janelle Rene Greenhill MPH		<input type="text"/> 07/11/2013	
20. Pre-application			
<input type="text"/>		<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>
		<input type="button" value="View Attachment"/>	

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Project/Performance Site Location(s)

Project/Performance Site Primary Location I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Research Foundation for Mental Hygiene, Inc.

DUNS Number: 1672049940000

* Street1: NYPI

Street2: 1051 Riverside Dr

* City: New York

County: New York

* State: NY: New York

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: 10032

* Project/ Performance Site Congressional District: NY-013

Project/Performance Site Location 1

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:

DUNS Number:

* Street1:

Street2:

* City:

County:

* State:

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code:

* Project/ Performance Site Congressional District:

Additional Location(s)

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved? Yes No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? Yes No

If yes, check appropriate exemption number. 1 2 3 4 5 6

If no, is the IRB review Pending? Yes No

IRB Approval Date: []

Human Subject Assurance Number: [00006105]

2. Are Vertebrate Animals Used? Yes No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? Yes No

IACUC Approval Date: []

Animal Welfare Assurance Number: []

3. Is proprietary/privileged information included in the application? Yes No

4.a. Does this Project Have an Actual or Potential Impact - positive or negative - on the environment? Yes No

4.b. If yes, please explain: []

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? Yes No

4.d. If yes, please explain: []

5. Is the research performance site designated, or eligible to be designated, as a historic place? Yes No

5.a. If yes, please explain: []

6. Does this project involve activities outside of the United States or partnerships with international collaborators? Yes No

6.a. If yes, identify countries: []

6.b. Optional Explanation: []

7. Project Summary/Abstract [abstract.pdf]

8. Project Narrative [projplan.pdf]

9. Bibliography & References Cited [ref.pdf]

10. Facilities & Other Resources [Facilities_Upload.pdf]

11. Equipment []

12. Other Attachments

Active psychosis in schizophrenia is among the most severe and burdensome medical conditions worldwide. However, the mechanisms of psychotic symptoms in this disorder, such as hallucinations (i.e., abnormal percepts in the absence of external sensory stimuli), remain elusive. This K23 application presents a research and training program that will support the applicant on a path towards becoming an NIH-funded independent investigator focused on the application of functional neuroimaging to the study of psychotic symptoms in schizophrenia. The activities in this application build on the candidate's prior training and are set in a resource-rich environment that will foster his development of expertise in (1) advanced analytic methods and study conduct for functional magnetic resonance imaging (fMRI) research; (2) computational neuroscience; (3) perception and cognition research; (4) pathophysiology and clinical assessment of schizophrenia; and (5) responsible and ethical conduct in scientific research with vulnerable populations. Combining functional magnetic resonance imaging (fMRI) and computational modeling, the current research proposal seeks to (1) define the neural mechanisms that generate hallucinations in schizophrenia; and (2) inform the development of a computational model of hallucinations based on *predictive coding*, an empirically-validated theoretical framework that supports a role of sensory systems in learning and predicting regularities in the external environment. The overarching hypothesis is that abnormal prediction-based attenuation of sensory cortical function produces excessive activity in the sensory cortex that generates hallucinations. To test this hypothesis, the present study will employ a novel speech discrimination fMRI paradigm, two groups of patients with schizophrenia, those with active, frequent auditory verbal hallucinations and those without a significant history of hallucinations, and a third group of healthy controls. This design will allow for testing a direct link between dysfunction in sensory predictive-coding mechanisms and the online experience of hallucinations in patients with schizophrenia, and will thus inform the neurobiological basis of psychotic symptoms in this disorder. Together, this training and research program will facilitate the candidate's transition to an independent research career and will help identify new therapeutic targets for refractory psychosis.

RELEVANCE: The novel application of the predictive-coding framework and model-based fMRI to the study of psychotic symptoms will shed new light on the mechanisms of generation of psychotic symptoms, thus filling an important gap in schizophrenia research. This project will serve to develop an *explanatory* model of hallucinations that can be used to generate specific, testable hypotheses for future neuroscience research in both humans and non-human animal models, and to uncover novel targets (sensory prediction deficits) likely modifiable by treatment via learning or pharmacotherapy.

PROJECT NARRATIVE

Schizophrenia poses a great social and economic burden in a significant percentage of patients who experience persistent symptoms, including increased risk for unemployment, homelessness, incarceration, chronic disability, and reduced life expectancy. As many as 30% of patients with schizophrenia experience persistent auditory hallucinations that are unresponsive to treatment. By elucidating the neurobiological mechanisms of hallucinations (and psychotic symptoms more generally), this project will contribute to a better understanding of schizophrenia and to the development of new treatment options to improve functional outcomes in refractory patients.

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RESOURCES

The activities of the **Department of Psychiatry at Columbia University** extend over three different, but closely integrated, institutions: 1) the New York State Psychiatric Institute (NYSPI), which has extensive research resources; 2) Columbia University Medical Center (CUMC), one of the largest providers of psychiatric services in New York City; and 3) Columbia University, which is responsible for training all disciplines in the behavioral sciences.

NYSPI has been one of the leading institutions for psychiatric research for over 100 years. Its resources, research faculty and staff, combined with those of the Research Foundation for Mental Hygiene's Division at NYSPI and Columbia University Department of Psychiatry, have made it one of the nation's most respected psychiatric research centers.

CUMC is at the world's forefront for patient care, biomedical research, and health science education. The nation's first academic medical center, CUMC was created in 1922 by an alliance between The Presbyterian Hospital and Columbia University's Health Sciences Division. This alliance has recently been enlarged by a merger between New York Hospital and Presbyterian Hospital in the City of New York with the newly named New York Presbyterian Hospital. Health Sciences at CUMC comprises the College of Physicians and Surgeons, the School of Dental and Oral Surgery, the School of Nursing, and the School of Public Health. Doctoral degrees from the Columbia University Graduate School of Arts and Sciences are offered in the Departments of Anatomy and Cell Biology, Biochemistry and Molecular Biophysics, Genetics and Development, Microbiology, Pathology, and Physiology and Cellular Biophysics. Relevant research institutes and centers based at Health Sciences include the Center for Community Health, Howard Hughes Medical Institute Program in Molecular Neurobiology, Howard Hughes Medical Institute Program in Structural Biology, Center for the Study of Society and Medicine, Irving Center for Clinical Research, and the Center for Medical Informatics.

The excellent climate for research training is reflected by the fact that the department houses a number of other NIMH-supported research-training programs (in psychiatric epidemiology, schizophrenia, anxiety and affective disorders, neurobiology, psychobiology, mental measurements, and HIV). The faculty members of these training programs are especially well supported to undertake research. Just in the Division of Child and Adolescent Psychiatry, in addition to the recent award of an NIMH-supported Intervention Research Center (IRC), there are more than *twenty different investigators* who are independently funded to do research in children and adolescents. Together they hold over *fifty-five research grants*, the majority of which are from federal sources, including NIMH, NIDA, SAMHSA, and CDC. The goals and methods used in this research are diverse and include methodologic, epidemiologic, clinical follow-up, biological, family-genetic, and treatment-and-prevention studies. The quality of training that the program has provided is evidenced by the number of development awards held by previous trainees in the program. They currently include nine recipients of Research Scientist Development Awards and one William T. Grant Scholar. Eleven recent graduates of the program have received R01s or NARSAD Young Investigator Awards. In addition to the Research Training in Child Psychiatry Program, the Child Psychiatry Division houses two clinical-training programs. These are the New York State Office of Mental Health-supported Child Psychiatry Clinical Training Program (twelve trainees; Training Director, Elisabeth Guthrie, M.D.) and the NIMH-supported Minority Training Program (four trainees; Training Director, Ian Canino, M.D.).

MRI UNIT AT COLUMBIA UNIVERSITY AND NEW YORK STATE PSYCHIATRIC INSTITUTE

NYSPI and Columbia University Department of Psychiatry 3.0 Tesla MRI Laboratory The MRI unit at the New York State Psychiatric Institute is the location of a 3T General Electric (GE) high performance MRI scanner. Dr. Andrew Gerber is Director of MRI Research in the unit. The site is state-of-the-art for image acquisition and analysis:

MRI Scanning Suite Our 3.0 T General Electric (GE) whole body scanner at NYSPI resides within a 3200 sq ft MRI Suite that includes the scanning room, a console area, a room dedicated for animal preparation, an electronics workshop, a laboratory for the design and construction of radiofrequency coils, a subject "ondeck" waiting area where scanning related tasks can be practiced and the procedures for the scan can be reviewed, a family waiting room, a wheelchair-accessible changing room and lavatory, a break room for the technologist and other staff, an office for the physicist, and a viewing room. The suite is equipped with 3 HP xw8000 workstations with full-image processing capabilities for all MRI modalities, 1 HP laser jet 1320n color printer, 2 Sun Ultra 60 workstations, and 6 Pentium-IV class PC's, each with 3GHz CPU, 2GB RAM, and 200 GB or more hard disk space. The MRI scanner and other hardware are described below. The unit is staffed with a full-time MRI technologist, a physicist, an electrical engineer who builds and maintains equipment and software used for physiological monitoring, and a full-time, dedicated pulse programmer. The scanning suite is located directly below the image processing laboratory, which has an Ethernet fiber optic connection directly to the scanning console. Transfer of large scale imaging data in variously formatted image files (DICOM, LX, GINX) from the MRI Unit to various computer platforms across laboratories of the institution will occur over dedicated fiberoptic network (with data transfer rate of 1 GBits/second) through a Storage Area Network (SAN). The SAN is a high-speed, special-purpose network that interconnects data storage devices with associated data servers of users on the network. SAN supports disk mirroring, backup and restore, archiving, and retrieval of archived data, data migration from one storage device to another, and the sharing of data among different servers. The SAN does not carry general-purpose traffic, such as, email or other end-user applications, and will avoid burdening a Local Area Network (LAN) with the data storage, retrieval and archival activities.

Whole Body 3T MRI Scanner The Signa 3.0 Tesla magnet, with a 55cm diameter patient bore, is a high homogeneity, actively shielded, wide-open superconducting system, utilizing single cryogen unit technology, which provides a very low boil-off rate. The magnet delivers high, uniform homogeneity (<0.05ppm on water spectral FWHM for 20cm DSV), which is essential for good image quality in demanding techniques such as spectroscopy and ultra-fast echo-planar imaging approaches. The high performance cardiac resonator module (CRM) gradient coil with enhanced gradient amplifiers can be operated at gradient amplitudes up to 4.0 mTesla/Meter with slew rates as high as 150 mTesla/Meter/mSec, which enables ultra-high spatial resolution (0.1 mm slice thickness in 3D) and ultra-fast imaging (34.0ms TR for 64 x 64 matrix EPI). Furthermore, 14 passive super-conducting shim coils improve the main field homogeneity up to <0.1ppm on the spectral width of an 8cc brain volume by high-order (up to 2nd order) automated resistive shimming. Four-channel fast receiver modules, along with an ultra low-noise digital RF subsystem and frequency synthesizer, and a quadrature-drive transmitter/receiver head coil, provide high SNR and stability (<0.05 ppm frequency variation, <5% amplitude variation, and <0.5 degree phase variation) to different neuroimaging studies. The camera room is actively shielded. The scanner's hardware and software are upgraded to GE's 16-channel HDx hardware platform, the EXCITE 3.0T head coils, and their ASSET (Array Spatial Sensitivity Encoding Technique) software. The 32 quadrature expandable channels and 16 high bandwidth receivers, along with ASSET, deliver cutting-edge parallel imaging by making

possible dramatically shortened TRs, TEs, and ESPs. Signal-to-noise is enhanced by approximately 100% over the prior LX platform, susceptibility artifacts are fewer, and resolution has been enhanced by these modifications. Furthermore, dual Intel Xeon 2.66GHz processors with 2GB host memory linked to an EXCITE vector array processor make simultaneous computing technology possible (400 images/s for 256 x 256 FFT), thereby benefiting real-time interactive imaging.

Planned Upgrade The New York State Psychiatric Institute has contracted with General Electric to install a state of the art GE 3 Tesla MR750 scanner in the existing space during summer 2013. This scanner will offer numerous advantages over the existing GE scanner while maintaining optimal compatibility at a field strength ideally suited for psychiatric brain imaging research. The MR750 will have improved gradients (50 mT/m with a slew rate of 200 T/m/sec), improved shimming (18 high order superconducting shim coils and 5 resistive shim coils), and choice of 32 channel (for best performance) and 8 channel (for best compatibility with the previous scanner) head coils. These combined advantages will offer a factor 2 to 8 improvement in scan times for existing sequences. Along with the new MR magnet, GE will be delivering the newest version of their console computer with an upgraded version of console software, as well as two image processing computers which will improve our ability for real time and post-scan processing of anatomic, functional, spectroscopic, and diffusion tensor imaging data. We anticipate that installation of the new magnet along with quality assurance testing will be completed by the end of August 2013 and investigators will resume a full scan schedule in September.

Small Animal MRI Scanner This is a state-of-the-art 9.4T/89mm Bruker vertical imaging system positioned in approximately 1300 sq. ft. of space on the 17th floor of the Black Building (Rm 1727). The unit consists of a Bruker MR micro 2.5 Gradient Technology with gradient sensitivities of 25 G/cm/A and with gradient strengths capable of up to 100 G/cm, as well as the ability to develop new pulse sequences within the Bruker ParaVision imaging software package. The gradient system is shielded by high performance technology and set against the gradient amplifiers. The system includes a Micro Mouse In Vivo Probe package, which includes a Micro AHS/RF 2.5 in vivo Probe with dual frequency mouse headresonator 1H/13C (20mm ID) and a Micro Mouse 2.5 in vivo Probe with dual frequency resonator 1H/23Na (30 mm ID). In addition, the scanner is equipped with two channel Receiver Modules, a low noise RF subsystem, and a frequency synthesizer. Fluothane anesthesia delivery system has been developed to control level of anesthesia from several minutes to several hours including physiological monitoring of rodents during imaging (pneumatic respiratory sensors, ECG sensors, RF filter, and monitor). The animal system also has an oximeter (SurgiVet V3304; Waukesha, WI), a ventilator (Harvard dInspira 55-7058; Harvard Apparatus, Holliston, MA), a Thermometer (Thermester YSI Precision 4000A; YSI Inc, Dayton, OH), and a Micro-Capnometer (Columbus Instruments, Columbus, OH). Finally, the facility houses a surgery room that contains all the necessary equipment, including a dissecting microscope, surgical tools, and anesthetic agents. Imaging data are easily off-loaded using FTP.

RF Coil Laboratory A design laboratory in the MRI unit houses electronic device building and repair. It consists of 400 sq ft area with bench space and tools storages and is equipped with electronics such as voltmeters, oscilloscopes, circuit design and construction, etc. It has the capability to design, construct and test electronic circuits. The laboratory has developed specialized coils, such as surface coils, dual tuned coils, and coils for fetal baboon imaging and GABA spectroscopy, which reduce RF inhomogeneities and susceptibility artifacts.

Comprehensive Image Acquisition Capabilities Multi-shot EPI sequences provide high-resolution functional applications (matrices up to 512 x 512) with FuncTool as a dynamic fMRI processing package. The Probe 2001 package enables proton spectroscopic applications on single voxel and multi-voxel (3D chemical shift imaging, i.e. CSI) basis. A multi-nuclear spectroscopy package and broadband RF amplifier for Phosphorous, Lithium, and Carbon is available. High B-value diffusion-weighted EPI technique with FLAIR preparation capabilities is installed, as is the latest Diffusion Tensor Imaging (DTI) acquisition package, spiral sequences, and perfusion imaging. Advanced vascular imaging includes Time-of-Flight (TOF) angiography and magnetization transfer contrast (MTC) methods. The GE MRI system also includes advanced image processing software, such as PROBE2000, PROBE 3D Brain, FuncTool, spiral, diffusion, fast spin echo, and Brain Wave packages. These permit easy visualization of single-voxel and multi-voxel spectra MRS data, 2D and 3D chemical shift imaging, parametric metabolite mapping, diffusion tensor post processing, functional brain mapping (BOLD), as well as fMRI stimulus sequencing and presentation.

Physiological Monitoring A Dell Pentium IV-class PC provides real-time recording of stimuli delivered to the subject and physiological monitoring of responses, such as manual responses, galvanic skin responses, and electrocardiography in the 3 Tesla MRI. An Invivo 3150 MRI Monitor system is available and will be used for monitoring and recording of electrocardiography (ECG), oxygen saturation, and oxygenation pulsation. All waveforms are sampled, displayed, and recorded through "Acknowledge" software. Several MRI-compatible multi-button response units, joystick and mouse are available. The system also runs E-Prime software, supplied by Psychology Software Tools, Inc. Visual stimulation is provided via projection from an Insight liquid crystal display (LCD) projector zoomed to a screen inside the MR suite. Dual channel binocular goggles (Model XAV-RTC2K; Resonance Technology, Inc.) are also available for visual stimulation with eye tracking capability. This unit utilizes optical fiber technology, which is robust to interference from MR gradient noise and operable in the strong magnetic field. It also provides independent visual input to each eye, which is a feature particularly important for fMRI applications. Audio stimulus presentation and subject communication are accomplished using headphones and microphone supplied by the GE medical system. The stimulus delivery and data recording systems are capable of synchronizing with MRI data acquisition. Also available is an MRI-compatible video camera for monitoring and recording of behaviors within the scanner during the scanning session.

MR Image Processing Laboratory This is located directly above the MRI scanning suite at NYSPI, where it occupies more than 2000 sq ft. The imaging laboratory currently has 3 Sun Ultra 1, 5 Sun Ultra 10, and 1 Sun Ultra 60 workstations, each with 256 MB RAM, dual 300-450 MHz sparc v9 floating point processors, 19-inch LCD color monitors, eight 75-gigabyte external hard drives for data storage, and an external optical drive. We also have 2 sun servers, SunFire V880, with dual 900 and 1200 MHZ CPUs, 4 GBytes of RAM, 850Gbytes of RAID5 hard disk storage along with an integrated fiber channel subsystem that provides an I/O performance of 1.2GB/sec. Additionally, 1 DELL PowerEdge 6600 server with 4 CPUs, 6 GB RAM, and 600 GB of disk space, running Microsoft Windows 2003, provides compute power and memory to even the most demanding image processing methods. 4.5 Terabytes high speed disk array are connected from SAN to the servers via 2G bps fiber channels. A Network-Attached Storage (NAS) with 3.75 Terabytes high-speed SCSI disk array is used for daily backup. A 1.9 Terabytes Tape library is also attached to the DELL server to perform monthly backup. This configuration of the servers provides the performance, speed, and storage required for real time patient image data analysis. The laboratory also houses 2 state-of-the-art Silicon Graphics workstations.

These workstations are seamlessly interconnected on the LAN to provide a distributed computing environment for the most efficient use of the computing power and the storage space by research assistants in our lab. This processing can be run in "batch" jobs in the background during the day, and in the foreground throughout the night when staff members are not using the workstations. This configuration of the servers provides the performance, speed, and storage required for real time patient image data analysis.

The lab also has 2 state-of-the-art Silicon Graphics workstations, 10 dual-processor Pentium IV PCs with 3.4G CPUs, 3G RAM, and 500GBytes hard disks, 12 Pentium-PC's, 3 Dell Inspiron Pentium laptops, 2 Macintosh laptops, 5 external optical drives, a HP LaserJet 4700dn color printer, a HP LaserJet 4250dn laser printer, a HP LaserJet 4100dn laser printer, a Lexmark C910 color printer and a Seiko Colorpoint 860 color printer. MR image analysis software includes ANALYZE, Matlab, SPM, MedX, and CARDVIEWS, which are installed and operational on all of these systems.

Personnel The laboratory has 11 full-time faculty members: 1 director (Dr. Peterson), 1 dedicated to anatomical and MR spectroscopy signal processing (Ravi Bansal, Ph.D.), 1 to diffusion tensor imaging (Dongrong Xu, Ph.D.), 1 to neuroimaging biostatistics (Jun Liu, Ph.D.), 1 to developmental cognitive neuroscience and neuroimaging (Rachel Marsh, Ph.D.), 1 to design and support electronic hardware for MRI and fMRI studies (Yunsuo Duan, Ph.D.), 1 to fMRI signal processing (Shan Yu, Ph.D.), 1 to pulse programming (Feng Liu, Ph.D.), 1 to MR Spectroscopy (Zhengchao Dong, Ph.D.), 1 to analysis of functional connectivity (Zhishun Wang, Ph.D.) and 1 high-field MRI physicist (Alayar Kangarlu, Ph.D.). The lab also currently has 5 postdoctoral and 3 pre-doctoral fellows. Twelve research assistants currently staff the workstations, and their activities are coordinated by a laboratory manager (Kathleen Durkin). The MR unit is staffed by a full-time MR technologist (Satie Shova) dedicated to data acquisition, transfer, and storage, as well as patient safety. The overall activities of all the laboratory personnel are coordinated by a laboratory administrator.

Network Support All personal computers are linked to a printer and to the computer network at the New York State Psychiatric Institute (NYSPI) as well as to Columbia University (CU). The study has access to all the network support made available by NYSPI and by the Division of Child Psychiatry at NYSPI. The libraries of both NYSPI and CU are available to the study, including all their on-line databases such as Medline, PsychInfo, PubMed, Health and Psychosocial Instruments, and many more. There is a copy center facility at NYSPI for heavy xeroxing of documents.

OTHER RESEARCH-DEDICATED MRI SCANNERS AT COLUMBIA UNIVERSITY

Hatch MR Center (Truman Brown, Director) approximately 6,000 sq-ft of newly renovated space in the basement of the Neurological Institute is under Dr. Brown's authority. The space contains a 1.5 T MR Research scanner and associated console, electronics and waiting areas. The research scanner is a Philips Intera and is fully equipped, with the cardiac imaging package, respiratory gating, all neuro sequences, 4 phased array coil detectors, a wide range of single and multiple coils and research keys so that new sequence development is possible.

fMRI Facility (Truman Brown, Director) This research-dedicated scanning suite is located on the lower level of the Neurological Institute building at 710 West 168th Street, adjacent to the Hatch MR Center. It houses a GE neurooptimized 1.5T MRI scanner equipped with echoplanar and parallel imaging capability.

OTHER RESEARCH DIVISIONS

Experimental Therapeutics (Daniel C. Javitt, MD, PhD, Director)

The Division of Experimental Therapeutics focuses on development of new treatment approaches for schizophrenia, depression and other severe mental disorders. This division was formed in 2011 by combining the Divisions of Brain Stimulation with a newly created Conte Center for Schizophrenia Research. The Division interacts closely with the Lieber Clinic to conduct early phase clinical studies of novel therapeutic agents, and with the C.O.P.E. Clinic to perform neurophysiological, neuroimaging treatment studies in the schizophrenia prodrome. The Columbia Conte for Schizophrenia Research conducts neurophysiological and neuroimaging investigations into brain mechanisms underlying schizophrenia and other severe mental disorders. Research activities are divided between Columbia University and Nathan Kline Institute for Psychiatric Research. The Center has been at the forefront of investigating the role of glutamatergic /N-methyl-D-aspartate receptor (NMDAR) dysfunction in the pathophysiology of schizophrenia, depression and other disorders and development of novel NMDAR based treatments. The Division interacts closely with the Lieber Clinic to conduct early phase clinical studies of novel therapeutic agents, and with the C.O.P.E. Clinic to perform neurophysiological, neuroimaging treatment studies in the schizophrenia prodrome.

Translational Imaging (Anissa Abi-Dargham, MD, Chief)

The area of research of the Division of Translational Imaging (DTI) at NYSPI is the development of novel tools and techniques to study neurotransmission in the living human brain, and the application of these techniques to clinical studies to unravel chemical imbalances associated with severe mental illnesses and drug addiction. Molecular imaging techniques based on Positron Emission Tomography (PET) are the main methods developed and used in the Division. The imaging approach has a translational emphasis, using imaging to identify phenotypes that can be tested in animal models or vice versa using models derived from preclinical knowledge to be tested in clinical populations. The faculty in the division are Lawrence Kegeles MD PhD, Mark Slifstein PhD and the Division Chief Anissa Abi-Dargham MD. Dr Slifstein is an internationally renowned expert in mathematical modeling and image analysis, Dr Kegeles has expertise in multimodal imaging including MRS, MRI and PET and Dr Abi-Dargham is internationally known for her contributions to understanding the neurochemistry of the brain in schizophrenia, particularly dopaminergic alterations and their modulation by NMDA dysfunction.

CLINICAL RESOURCES

New York State Psychiatric Institute and Columbia University Department of Psychiatry

New York State Psychiatric Institute and Columbia University Department of Psychiatry In June 1998, the Child Research Clinic, which consists of Clinical Core and support staff, moved its operation to a new Psychiatric Institute Research building on an adjacent site. The Clinical Core occupies 871 square feet in this new building. The new space is more centralized and highly conducive to collaboration between investigators.

Lieber Schizophrenia Research Clinic

The Lieber Schizophrenia Research Clinic (LSRC) is located at the New York State Psychiatric Institute (NYSPI) on the Columbia-Presbyterian Medical Campus. The clinic provides outpatient services to individuals participating in research studies conducted by NYSPI and Columbia faculty investigators. Only individuals willing to participate in research are considered for

admission to the clinic. The clinic supports a number of research studies designed to answer questions about the nature and causes of schizophrenia and optimal treatment approaches. Currently, the clinic follows over 70 outpatients regularly, all of whom participate in research studies.

Washington Heights Community Service

The Washington Heights Community Service (WHCS) is a comprehensive community-based program for individuals with severe mental illness who live in Northern Manhattan. The Service consists of a 22-bed inpatient unit at NYSPI and two outpatient clinics located in the communities of Washington Heights (Audubon Clinic) and Inwood (Inwood Clinic) that serve approximately 1,000 people. The inpatient unit provides treatment for a variety of psychiatric illness, with a majority of people receiving treatment for a psychotic disorder (e.g., Schizophrenia or Schizoaffective Disorder) or a major affective disorder (e.g., Bipolar Disorder or Major Depression). Most people discharged from the inpatient unit are referred to one of the two WHCS outpatient clinics, where they continue to receive culturally sensitive, personalized, comprehensive psychiatric care from psychiatrists and other mental health professionals, many of whom have faculty appointments in the Columbia University Medical School.

BIOSTATISTICAL RESOURCES

The Biostatistics Division at the New York Psychiatric Institute (NYSPI) provides researchers access to and training in state-of-the-art statistical techniques as needed for optimal use of their research data. The Division's activities include developing and applying new methodologies for the design and analysis of psychiatric studies, participating in major, funded research projects, teaching statistics to researchers and fellows of training grants, mentoring PhD candidates from the Department of Biostatistics at the Mailman School of Public Health at Columbia University in methodological topics related to neuropsychiatric research, and providing consultations on data-analytic and design issues for grant submission and manuscript preparation.

The Biostatistics Division, through an NIMH-funded CoGENT grant (Core Grant to Enhance Neuroscience Transfer), has created an environment for theoretical research on statistical methods required to analyze brain imaging data. The Biostatistics Division has a group of devoted statistical experts, Drs. Naihua Duan (Director), Todd Ogden, Jun Liu, and Huiping Jiang, that develops theory adequate to the respective brain imaging technology and creates computer programs to implement the theoretical methods.

Because of the close ties between NYSPI and Columbia University, the Biostatistics Division has strong support of the Department of Biostatistics at Columbia University, where Dr. Ellis and Ogden are also faculty members. The Department of Biostatistics has a large faculty with expertise in diverse areas of statistics: clinical trials, analysis of microarray data, statistical genetics, neuroimaging data analysis, methods for handling missing data in medical research, clustered and longitudinal data analysis, categorical data analysis, multivariate analysis, meta-analysis and many others. These methods and developed programs are available to researchers at the NYSPI to help them answer their research questions.

COMPUTER

The **Brain Imaging Laboratory** and **MRI Unit** has Local Area Networks (LANs) which are in turn connected to the New York State Psychiatric Institute's Wide Area Network (WAN). The file server (NYSPI.CPMC.COLUMBIA.EDU) is a Dell PowerEdge 1800 Server, with dual Intel Xeon Processor at 2.8GHz/2MB Cache, 800MHz FSB, 2GB DDR2 of RAM and a 300 GB hard drive, running MS Windows Server 2003 (licensed 50 users) and MS SQL Server 2005. The file server

also serves as a printer server, to which an HP Laserjet 3005 printer is attached. A Dell PowerEdge SC440, with Pentium (R) at 2.8GHz/2MB Cache, 800MHz FSB, 1GB DDR2 of RAM and a 260GB hard drive, is servicing our GroupWise Post Office. Software used throughout the network includes: Microsoft SQL Server 2005, Microsoft Office 2000/2003 Professional Edition including Access, Excel, Powerpoint and Word, Corel Wordperfect Suite 10, Microsoft FoxPro, SPSS, SAS, and GroupWise Client v7. In the NYSPI Computer Center, Computer services are available free of charge to all participating investigators. The Computer Center has an IBM-4381-11 mainframe computer that provides both interactive and batch processing. It has BMDP and LISREL statistical software packages. Personnel at the Computer Center include statisticians, programmers, and data entry clerks.

The **Division of Translational Imaging** is also equipped with 16 Macintosh computers: 5 iMac desktops and 11 Macintosh MacBook and MacBookPro laptops for individual use of all senior personnel and postdoctoral fellows for document processing and data analysis. These are backed up wirelessly using Macintosh Time Capsule and Time Machine software. Additionally, there are 3 laser printers (1 HP, 1 Lexmark and 1 Xerox), one facsimile machine with a top-load sheet feeder, and one Xerox photocopier with top-load sheet feeder. Furthermore, the clinical research team is equipped with 4 MacBook computers with Intel Dual Processors, which run the neuropsychological testing battery based in PsyScope software. In addition there is one Dell Latitude D350 PC running the MATRICS battery as well as the neuropsychological testing battery based in eprime.

OFFICE

Office space is available for the Dr. Horga, mentoring team, and staff. All investigators have permanent office space at NYSPI. Clinical offices are located on the 4th and 5th floors of NYSPI and investigator office space is located on the 6th floor of NYSPI and the 4th floor of the Kolb Annex to NYSPI. The Division of Translational Imaging occupies a suite of 10 large offices on the 4th floor of the Kolb Annex, in addition to 2 large data analysis rooms with multiple workstations and a clinical examination room. All imaging analyses and subject screening will be performed in these facilities.

In particular, Dr. Horga's office is located in the Division of Translational Imaging on the 6th floor of the NYSPI, in close proximity to all facilities described herein and to the private offices of Drs. Peterson, Abi-Dargham, and Javitt. These are also adjacent to the Brain Imaging laboratory on the 2nd floor of NYSPI and next to the Division of Experimental Therapeutics (5th floor of NYSPI) and the Division of Translational Imaging (6th floor of NYSPI) where Drs. Javitt and Abi-Dargham, respectively, have private offices. The Lieber Schizophrenia Research Clinic is also located in the same building. The offices (roughly 300 sq. ft. each) are equipped with a phone, a desktop computer, filing cabinets, and internet connectivity. Research assistants (clinical and image analysts) will have offices on the 6th floor of NYSPI, within proximity of Dr. Horga and the Brain Imaging laboratory.

OTHER FACILITIES

All personnel have use of the **Columbia University Health Sciences** and **New York State Psychiatric Institute Libraries**. The former contains over 400,000 volumes, 3800 periodicals, microfiche/film reading and copying equipment, and extensive data base services. The latter contains over 30,000 volumes and 400 journals in the areas of psychology, psychiatry, and neuroscience. Also, the **Photocopy Center** and **Department of Medical Illustration** at the New York State Psychiatric Institute are available for use.

OTHER LABORATORIES

The research laboratories of the Psychiatric Institute comprise approximately 400 rooms and 90,000 square feet of space. The building houses offices, laboratories, support services, observation rooms, conference teaching rooms, two floors of animal quarters, and animal testing and operating areas.

Molecular Genetics Laboratory: The molecular genetics unit, under the direction of Dr. L. Erlenmeyer-Kimling consists of three contiguous laboratories that occupy 2,200 square feet. The labs are composed of a complete tissue culture facility where over 9,000 lymphoblast cell lines have been virally transformed; a dark room facility; walk-in cold room; microscope room; radioactivity room and three biochemistry labs.

Analytical Chemistry: Approximately 2000 square feet of wet laboratory space plus office space are devoted to the Analytical Psychopharmacology Laboratory, under the direction of Thomas B. Cooper. The laboratory is equipped to handle clinical pharmacology experimental protocols, including: 1) pharmacokinetic and pharmacodynamic studies of novel psychotropic drugs; 2) assays of all psychoactive drugs (e.g. heroin, cocaine, methadone) in current use, together with psychoactive metabolites; and 3) biological challenge studies controlled by drug plasma level monitoring. Analytical instrumentation includes GLC, HPLC, and a variety of detectors together with a GC/MS and EI, CI, NCI and SIM capabilities. A large variety of receptor drug and drug metabolite assays are routinely performed in biological studies paradigms. The laboratory is well equipped and highly automated as more than 20,000 assays of drugs and metabolites and neuroendocrine measures have been performed in each of the last several years.

Biological Studies Unit (BSU): The Biological Studies Unit under the direction of Dr. Laszlo Papp, occupies approximately 1,600 square feet of laboratory space. It comprises six patient rooms and two monitoring rooms. The BSU is part of the Department of Therapeutics at NYSPI. The Unit is a multipurpose research facility that provides state-of-the-art technology for complex biological and psychophysiological studies. The BSU has been involved in research into the psychobiology of anxiety and affective disorders. Major Resources & Equipment includes a wet laboratory with Laminar sterile bench, seven Grass Model 12channel Polygraph; MNC Digital computer; a Vetter FM recorder; Respirtrace ventilatory monitoring equipment; Kendall automated sphygmomanometer; VCR with camera and monitor, and microcomputer for stimulus generation.

Additional Available Laboratories Include:

Analytical Psychopharmacology (Thomas Cooper)

Anxiety Disorders Clinic (Blair Simpson)

Biological Psychiatry (Steven Roose)

Biometrics (Robert Spitzer)

Child Psychiatry (David Shaffer)

Clinical Neuropsychiatry (Sukdeb Mukherjee)

Clinical Psychopharmacology (Alexander Glassman)

Clinical Therapeutics (B. Timothy Walsh)

Communications Science (Joseph Jaffe)

Depression & Eating Disorders Research Unit (Evelyn Attia)

Depression Evaluation Service (Patrick McGrath, Jonathan Stewart)

Development Psychobiology (Myron Hofer)

Developmental Behavioral Studies (L. Erlenmeyer-Kimling)

Developmental Psychoendocrinology (Heino F. L. Meyer-Bahlburg)

Epidemiology of Brain Disorders (Ezra Susser)

Epidemiology of Mental Disorders (Elmer Struening)
Genetics and Development (Gerard Karsenty)
Geriatrics and Gerontology (Barry Gurland)
Medical Genetics (L. Erlenmeyer-Kimling)
Molecular Imaging and Neuropathology (John Mann)
Pathology & Cell Biology (James Goldman)
Physiology & Cellular Biophysics (Andrew Marks)
Psychogenetics (Miron Baron)
Psychophysiology (Gerard Bruder)
Research Assessment & Training (Jean Endicott)
Social Psychiatry (Bruce Dohrenwend)

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

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Degree Type:					
Degree Year:					
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Attach Current & Pending Support			Add Attachment	Delete Attachment	View Attachment

PROFILE - Senior/Key Person 1

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Degree Type:					
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*Attach Biographical Sketch		Bio_Dr._Bradley_Peterson_1.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support			Add Attachment	Delete Attachment	View Attachment

RESEARCH & RELATED Senior/Key Person Profile (Expanded)**PROFILE - Senior/Key Person 2**

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Degree Year:		
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PROFILE - Senior/Key Person 3

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Degree Type:		
Degree Year:		
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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Horga Hernández, Guillermo, M.D., Ph.D.*	POSITION TITLE Assistant Professor**		
eRA COMMONS USER NAME (credential, e.g., agency login) GHORGA			
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.</i>)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Universidad Miguel Hernández of Elche, Spain Hospital Clínic of Barcelona, Barcelona, Spain University of Barcelona, Barcelona, Spain Columbia University, NY	M.D. Residency Ph.D. Fellowship	05/04 05/09 07/13* 06/12	Medicine and Surgery Psychiatry Clinical Neuroscience Psychiatric research

*Expected date of Ph.D. thesis defense and degree conferral: October, 2013; **Starting September, 2013

A. Personal Statement

I am an Associate Research Scientist and will start as Assistant Professor in Clinical Psychiatry in September 2013 in the Division of Translational Imaging at Columbia University and the New York State Psychiatric Institute. I am trained as a psychiatrist and recently completed a postdoctoral research fellowship with Dr. Brad Peterson, where I applied functional neuroimaging methods to the mechanistic study of cognition and learning in health and mental illness. This K23 award application builds on my prior training by providing intensive mentored and hands-on study in functional neuroimaging experimentation, computational-modeling methods, and the neuroscience of cognition and perception. The proposed research, "Neural mechanisms of sensory predictions in schizophrenia with auditory hallucinations," will use functional neuroimaging to study predictive sensory signals underlying the generation of hallucinations in patients with schizophrenia. Access to the wealth of resources available at Brad Peterson's laboratory, the Lieber Schizophrenia Research Clinic and the New York State Psychiatric Institute in combination with direct mentorship by leading schizophrenia and clinical neuroimaging researchers will supplement my demonstrated research and leadership skills, high level of motivation, and creativity, to assure the successful completion of the proposed research. This research and training will prepare me for initiating an independent career focused on clinical and advanced neuroimaging research in schizophrenia.

B. Positions and Honors

Positions and Employment

2005-2009	Psychiatry resident, Hospital Clínic of Barcelona, Spain
2008	Visiting scholar, PET Lab, Mount Sinai School of Medicine, NY
2009-2012	Post-doctoral research fellow, Columbia University, NY
2012-2013	Associate Research Scientist, Columbia University, NY
2013-	Assistant Professor in Clinical Psychiatry, Columbia University, NY

Other Experience and Professional Memberships

2009-	Society for Neuroscience, member
2009-	Organization for Human Brain Mapping, member
2009	Medical Trends S.L., Barcelona, Spain, scientific coordinator and translator
2010-	Neuroscience and Biobehavioral Reviews, Psychiatry Research, Schizophrenia Research, CANN, Organization for Human Brain Mapping Annual Meeting, Journal of Child Psychology and Psychiatry, Journal of Psychiatric Research, Springer Verlag, ad-hoc reviewer

Honors and Awards

1999	Erasmus Programme award for stay at Mainz University, Germany
2005	Extraordinary Award in Medicine, UMH (equivalent to summa cum laude)
2005	Scored in the 99th percentile of the Spanish national medical residency entrance exam (MIR exam)
2007	Dr. Novoa Santos-Lilly Prize, Spanish National Psychiatry Meeting 2007
2008-2009	Chief Resident in Psychiatry, Hospital Clinic of Barcelona, Spain
2008	Spanish National Psychiatry Residents Prize
2012	Bodini fellowship award (Italian Academy for Advanced Studies in America, Columbia University, NY)

C. Peer-Reviewed Publications (in chronological order, from 18 publications)

1. **Horga G**, Horga JF. [Adverse cardiac events associated with the use of clozapine]. *Bol Farmacovig CV*, 2008;1(70):5-7.
2. Baeza I, Pons A, **Horga G**, Bernardo M, Lázaro ML, Castro-Fornieles J. Electroconvulsive therapy in early adolescents with schizophrenia spectrum disorders. *J ECT* 2009 Dec;25(4):278-9.
3. Mané A, Falcon C, Mateos JJ, Fernandez-Egea E, **Horga G**, Lomeña F, Bargalló N, Prats-Galino A, Bernardo M, Parellada E. Progressive gray matter changes in first episode schizophrenia: a 4-year longitudinal magnetic resonance study using VBM. *Schizophr Res* 2009 Oct;114(1-3):136-43.
4. Fernandez-Egea E, Parellada E, Lomeña F, Falcon C, Pavia J, Mane A, **Horga G**, Bernardo M. (18)FDG PET study of amygdalar activity during facial emotion recognition in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2010 Feb;260(1):69-76.
5. Baeza I, Flamarique I, Garrido JM, **Horga G**, Pons A, Bernardo M, Morer A, Lázaro ML, Castro-Fornieles J. Clinical experience using ECT in adolescents with schizophrenia spectrum disorders. *J Child Adolesc Psychopharmacol* 2010 Jun;20(3):205-9.
6. **Horga G**, Horga A, Baeza I, Castro-Fornieles J, Pons A. Drug-induced speech dysfluency and myoclonus preceding generalized tonic-clonic seizures in an adolescent male with schizophrenia. *J Child Adolesc Psychopharmacol* 2010 Jun;20(3):233-4.
7. **Horga G**, Parellada E, Lomeña F, Fernández-Egea E, Mané A, Font M, Falcón C, Konova A, Pavia J, Ros D, Bernardo M. Differential brain glucose metabolic patterns in antipsychotic-naïve first episode schizophrenia with and without auditory verbal hallucinations. *J Psychiatry Neurosci* 2011 Jan 1;36(1):100085.
8. **Horga G**, Bernacer J, Dusi N, Entis JJ, Kingwai Chu, Hazlett EA, Haznedar MM, Kemether E, Byne W, Buchsbaum MS. Correlations between ventricular enlargement and gray and white matter volumes of cortex, thalamus, striatum and internal capsule in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2011 Mar 24. PMCID: PMC3182327
9. Marsh R, **Horga G**, Wang Z, Wang PW, Klahr KW, Berner LA, Walsh BT, Peterson BS. An fMRI study of self-regulatory control and conflict resolution in adolescents with Bulimia Nervosa. *Am J Psychiatry* 2011 Nov;168(11):1210-20. Epub 2011 Jun 15. PMCID: PMC3328859
10. Mané A, Mateos JJ, Gallego J, **Horga G**, Fernández-Egea E, Lomeña F, Ros D, Pavia J, Bernardo M, Parellada E. Dopamine transporter and schizophrenia outcome: a 4-year follow-up DAT-Scan study in first episode schizophrenia. *Psychiatry Res* 2011 Oct 31;194(1):79-84.
11. **Horga G**, Maia TV, Wang P, Wang Z, Marsh R, Peterson BS. Adaptation to conflict via context-driven anticipatory signals in the dorsomedial prefrontal cortex. *J Neurosci* 2011 Nov 9;31(45):16208-16. PMCID: PMC3244974
12. Fernández-Egea E, Parellada E, Sugranyes G, **Horga G**, Lomeña F, Falcon C, Pavia J, Bernardo M. Left Amygdalar Activation With Deficit Syndrome compared to Non-Deficit Subjects During the Control Task in a Facial Emotion Recognition Paradigm. *Psychiatry Res* 2012 Aug 3.
13. **Horga G**, Maia TV. Conscious and unconscious processes in cognitive control: a theoretical perspective and a novel empirical approach. *Front Hum Neurosci* 2012 Jul 4 6:199. PMCID: PMC3458455

14. Marsh R, **Horga G**, Parashar N, Wang Z, Peterson BS, Simpson HB. Altered Activation in Fronto-Striatal Circuits During Sequential Processing of Conflict in Unmedicated Adults with Obsessive-Compulsive Disorder. *Biol Psychiatry*. 2013 Mar 12.
15. **Horga G**, Kaur T, Peterson BS. Current Limitations and Future Directions in MRI studies of Developmental Psychopathologies. *J Child Psychol Psychiatry*. 2014 (in press)

Research Support

Ongoing Research Support

07/01/13-07/01/15

CTSA/Irving Institute TRANSFORM K12 Award, Irving Institute for Clinical and Translational Research, Columbia University, New York, NY

Pending Support

NARSAD Young Investigator Award 2013 (PI: Horga), "Neural mechanisms of transcranial direct current stimulation for the treatment of schizophrenia"

NARSAD Distinguished Investigator Award 2013 (PI: Javitt, Investigator: Horga), "N-channel tDCS stimulation for treatment of persistent AVH in Schizophrenia"

Completed Research Support

05/01/08-09/31/08

Astra-Zeneca/Fundación Española de Psiquiatría y Salud Mental grant for external rotation at Mount Sinai Hospital, NY (extra-mural competitive grant for Spanish psychiatrists)

07/01/09-07/01/11

Alicia Koplowitz Foundation grant for Child and Adolescent Psychiatry research fellowship (extra-mural competitive grant for Spanish psychiatrists)

09/01/12-06/01/13

Bodini fellowship from the Italian Academy for Advanced Studies in America, Columbia University, NY

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Bradley Scott Peterson	POSITION TITLE Suzanne Crosby Murphy Professor with Tenure		
eRA COMMONS USER NAME (credential, e.g., agency login) PETERSONOB			
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.</i>)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Tulane University (Summa Cum Laude) Oxford University University of Wisconsin-Madison Medical School University of Wisconsin-Madison Hospital Massachusetts General Hospital Yale Child Study Center Yale Child Study Center	BA MD	1979-1983 1981-1982 1983-1987 1987-1988 1988-1990 1990-1992 1992-1994	Philosophy Philosophy & Chemistry Medicine Medicine Internship General Psychiatry Postdoctoral Research Child Psychiatry

A. Statement

I am Director of the Center for Developmental Neuropsychiatry in the Department of Psychiatry at Columbia University and New York State Psychiatric Institute. I have a long history of studying the neurobiological basis of a wide range of serious neuropsychiatric disorders, including Autism Spectrum Disorders, in children, adolescents, and adults.

B. Positions and Honors**Positions and Employment**

1993-2001	Director of Neuroimaging, Yale Child Study Center
1994-2000	Assistant Professor Child Psychiatry, Yale Child Study Center
1996-2001	Elizabeth Meers and House Jameson Assistant Professor, Yale Child Study Center
1999-2000	Associate Professor Child Psychiatry & Diagnostic Radiology, Yale University School of Medicine
2000-2001	Associate Professor Child Psychiatry & Diagnostic Radiology, Yale University School of Medicine
2001-2005	Suzanne Murphy Associate Professor, Columbia University
2002-2012	Director of MRI Research, Columbia University & NY State Psychiatric Institute
2005-present	Suzanne Murphy Professor with Tenure, Columbia University
2008-2012	Chief, Division of Child and Adolescent Psychiatry, Columbia University
2012-present	Director, Center for Developmental Neuropsychiatry

Other Experience and Professional Memberships

2001-2009	Co-Deputy Director, NIMH-Sponsored Post-Doctoral Training Program (T-32)
2006-present	Full Member, American College of Neuropsychopharmacology (ACNP)
2010-present	Director, NIMH-Sponsored Post-Doctoral Training Program (T-32)

Honors

1983	Summa Cum Laude with Departmental Honors in Philosophy at Tulane University
1983	Phi Beta Kappa Honors Society
1986	Alpha Omega Alpha Medical Honors Society, Junior Year
1987	American Medical Association Rock Sleyster Memorial Scholarship in Psychiatry
1992	The Society of Biological Psychiatry Dista Fellowship Award
1992	American Academy of Child and Adolescent Psychiatry Presidential Scholar Award for Research
1993	American Academy of Child & Adolescent Psychiatry Robinson Cunningham Award, best paper
2002-2011	<i>Best Doctors in America</i>

C. Selected Peer-reviewed Publications (from more than 230, most relevant to current application)

1. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span: nonlinear age effects on gray matter. *Nature Neurosci*, 6:309-315, 2003. PMID:12548289
2. Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peterson BS. Cortical abnormalities in children and adolescents with Attention Deficit Hyperactivity Disorder. *Lancet*, 362:1699-1707, 2003. PMID:14643117
3. Sowell ER, Kan E, Yoshii J, Thompson PM, Bansal R, Xu D, Toga AW, Peterson BS. Thinning of gray matter in the sensorimotor cortices of children with Tourette syndrome. *Nat Neurosci*, 11:637-639, 2008. PMID:18488025.
4. Peterson BS, Warner V, Bansal R, Zhu H, Hao X, Liu J, Durkin K, Adams PB, Wickramaratne P,
 - a. Weissman MM. Cortical thinning in persons at increased familial risk for major depression. *PNAS*, 106:6273-6278, 2009. PMCID: PMC2669378
5. Posner J, Russell J, Gerber A, Colibazzi T, Gorman D, Yu S, Wang Z, Kangarlu A, Zu H, Peterson BS. The neurophysiological bases of emotion: an fMRI study of the affective circumplex using emotion-denoting words. *Hum Brain Mapping*, 30:883-95, 2009. PMID:18344175
6. Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, Plessen KJ, Yu S. An fMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. *Am J Psychiatry*, 166:1286-1294, 2009. PMID:19755575
7. Sobel LJ, Bansal R, Maia TV, Sanchez J, Mazzone L, Durkin K, Liu J, Hao X, Ivanov I, Miller A, Greenhill LL, Peterson BS. Surface morphology of the basal ganglia and the effects of stimulant medications in children with Attention-Deficit/Hyperactivity Disorder. *Am J Psychiatry*, 167:977-86, 2010. PMID:20595414
8. Marsh R, Hao X, Xu D, Wang Z, Packard MG, Duan Y, Liu J, Kangarlu A, Martinez D, Garcia F, Tau G, Yu S, Peterson BS. A virtual reality-based fMRI study of reward-based spatial learning. *Neuropsychologia*, 48:2912-21, 2010. PMID:20570684
9. Mazzone L, Yu S, Blair C, Gunter BC, Marsh R, Peterson BS. An fMRI study of frontostriatal circuits during the inhibition of eye blinking in persons with Tourette syndrome. *Am J Psychiatry*, 167:341-349, 2010. PMID:20080981
10. Wang Z, Maia T, Marsh R, Colibazzi T, Gerber A, Peterson BS. The neural circuits that generate tics in Gilles de la Tourette syndrome. *Am J Psychiatry*, 168:1326-1337, 2011. PMID:21955933
11. Horga G, Maia T, Wang PW, Wang Z, Marsh R, Peterson BS. Adaptation of response conflict via context-driven anticipatory signals in the dorsomedial prefrontal cortex. *J Neuroscience*, 31:16208-16, 2011. PMID:22072672.
12. Rauh VA, Horton M, Perera F, Whyatt R, Bansai R, Hao X, Liu J, Slotkin TA, Peterson BS. Abnormalities of brain structure in children exposed prenatally to chlorpyrifos, a common organophosphate insecticide. *PNAS*, 109:7871-7876, 2012. PMID:22547821
13. Hao X, Xu D, Bansal R, Dong Z, Wang Z, Liu J, Kangarlu A, Liu F, Duan Y, Shova A, Peterson BS. Multimodal Magnetic Resonance Imaging: The coordinated use of multiple, mutually informative probes to understand brain structure and function. *Hum Brain Mapping*, 34(2):253-71, 2013. PMID:22076792
14. Posner J, Hellerstein D, Gat I, Mechling A, Klahr KW, Wang Z, McGrath P, Stewart J, Peterson BS. Antidepressants normalize the default mode network in patients with dysthymia. *Arch Gen Psychiatry*, in press.

D. Research Support

Active Research Support

2 T32 MH16434-31 (B. Peterson, PI)

07/01/10-06/30/15

NIMH

Translational Research Training in Child Psychiatry

The program trains postdoctoral psychiatrists, psychologists, and developmental neuroscientists to become investigators in translational neuroscience research of child and adolescent psychiatric disorders. The

grant supports ten M.D. and/or Ph.D. trainees for up to three years.

Role: Principal Investigator

The Simons Foundation Simons Simplex Family Resource (B. Peterson, PI) 11/01/06-03/31/14

The aim of the resource is to rapidly collect 1000 standard set of phenotypic data from proband with Autism or Autism Spectrum Disorder (ASD) and at least one full sibling without evidence of Autism or ASD, and two biological parents who are unaffected.

Role: Principal Investigator

1 R01 ES015579-01 (V. Rauh, PI) 03/01/09-11/30/13

NIH/DHHS

Assess the effects of pre- and postnatal exposure to the organophosphorus pesticide, chlorpyrifos (CPF). The purpose of this study is to assess the effects of pre- and postnatal exposure to the organophosphorus (OP) pesticides chlorpyrifos (CPF) and diazinon on neurobehavioral functioning in a cohort of inner-city children who have reached 8-9 years of age.

Role: Co-Investigator

1 R01 MH36197-15 (M. Weissman, PI) 07/01/10-06/30/15

NIMH

Children at High and Low Risk for Depression

This study aims to identify the brain-based correlates of children and adults at high or low risk for depressive illness using anatomical and functional MRI.

Role: Co-Principal Investigator

R01DA027100 (V. Rauh & B Peterson, Co-PIs) 07/01/10-06/30/15

NIDA

Impact of Prenatal and Early Childhood Environmental Tobacco Smoke Exposure on Brain Development
The purpose of this study is to assess the effects of prenatal and early childhood exposure to environmental tobacco smoke (ETS) on brain structure and function in a cohort of 250 inner-city children who are 9-10 years of age. We will use MRI to study detailed brain anatomy, fiber tracts, and metabolites in these children, and we will assess cognitive and attentional functioning using an array of neuropsychological tasks.

Role: Co-Investigator

1 P50 MH090966-01 (J. Gingrich, PI) 07/01/10-06/30/15

NIH/NIMH

Silvio O. Conte Centers for Basic and Translational Mental Health Research Serotonergic Modulation of Brain Development: Genetic and Pharmacologic Influences on Structure, Function, and Behavior

Several lines of evidence indicate that in species from rodents to humans, serotonin acts as a neural growth factor during early phases of brain maturation to influence brain structure, neurophysiology, and ultimately behavior. Serotonin signaling can be affected by either genetic (5httlpr) or pharmacologic (SSRI, MAOI) variables during early life. We hypothesize that low-expressing 5httlpr variants of the serotonin transporter (SERT) and pharmacologic inhibition of SERT function produce similar effects on brain maturation and ultimately behavior and increase the risk for clinical diagnoses such as affective and anxiety-related disorders.

Role: Principal Investigator of Conte Project 3

Co-Principal Investigator of Core Imaging

1 R01 MH093677-01A1 (C. Monk & B. Peterson, PI) 09/23/11-06/30/16

NIMH

The Effects of Prenatal Stress & Poor Nutrition on Brain and Cognition

The goal of this project is to assess the influence of maternal prenatal self-reported stress and endocrine activity, as well as poor nutrition, on neonatal brain structure and function, and to relate the imaging measures to cognitive outcomes in early childhood.

Role: Co-Investigator

1 R01 MH096334-01 (G. Siegle, PI)

07/07/12-06/30/17

NIH

Blunted and Discordant Affect Syndrome: A transdiagnostic construct in Psychopathology

Assess the validity of a blunted and discordant affect (BADA) construct in multiply- symptomatic pan-diagnostic individuals stratified on abuse history and diagnosis, compared to healthy individuals.

Role: Sub-contract Principal Investigator

Completed Research Support

NIMH 2R01MH06482407 (W. Kates, PI)

08/05/07-06/30/12

Biomarkers for Psychosis in Velocardiofacial Syndrome (Subcontract)

This project continues the longitudinal study of risk factors for psychosis in velocardiofacial syndrome (VCFS), a relatively common disorder caused by a microdeletion on chromosome 22q11.2.

Role: Co-Investigator

NARSAD Distinguished Investigator Award (B. Peterson, PI)

07/01/10-06/30/12

Use of a Brain-Based Biomarker in the Prevention and Treatment of Adolescents with Major Depression

This study will use psychotherapy or medication to prevent or treat depression in adolescents who have right hemisphere cortical thinning, a biomarker for familial depression.

Role: Principal Investigator

NIMH 1 K02 MH074677 (B. Peterson, PI)

07/01/05-06/30/11

MRI In Childhood Neuropsychiatric Disorders

This is a midlevel Career Development Award to use Magnetic Resonance Imaging (MRI) methodologies to identify the neurobiological basis of developmental neuropsychiatric disorders.

Role: Principal Investigator

NIMH R01 MH089582 (B. Peterson, PI)

10/01/09-08/31/12

Identifying Brain-Based Biomarkers for ASD & their Biological Subtypes

The goal of this research program is to identify brain biomarkers of Autism Spectrum Disorders (ASDs) and biologically-based ASD subtypes using multimodal Magnetic Resonance Imaging (MRI).

Role: Principal Investigator

NIMH 1 K02 MH074677 (B. Peterson, PI)

07/01/05-06/30/10

MRI In Childhood Neuropsychiatric Disorders

This is a midlevel Career Development Award to use Magnetic Resonance Imaging (MRI) methodologies to identify the neurobiological basis of developmental neuropsychiatric disorders.

Role: Principal Investigator

1 R01 DA017820 (B. Peterson, PI)

09/01/04-05/31/10

MRI of Infants Exposed Prenatally to Drugs of Abuse to define the effects of drugs of abuse on brain structure and metabolite concentrations, as well as the behavioral correlates of those effects, in infants and children who have been exposed to drugs of abuse during fetal development.

Role: Principal Investigator

1 R01 MH068318 (B. Peterson, PI)

09/30/04-06/30/10

Neuroanatomical MRI Studies of Childhood Disorders to understand normal brain development and the neural basis of childhood neuropsychiatric disorders using anatomical MRI.

Role: Principal Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Abi-Dargham, Anissa	POSITION TITLE Professor of Clinical Psychiatry Chief, Division of Translational Imaging Associate Director of Columbia Univ PET Center		
eRA COMMONS USER NAME (credential, e.g., agency login) AA324X			
<i>EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
St. Joseph University, Beirut, Lebanon	M.D.	1984	Medicine

A. Personal Statement

I am Chief of the Division of Translational Imaging and Associate Director of the PET Center at Columbia University and New York State Psychiatric Institute. My research has mostly focused on using molecular imaging techniques (SPECT and PET) to study the pathophysiology of schizophrenia, in particular the role of dopamine dysfunction in schizophrenia and its relationship to cognition and response to treatment. For this grant, I will mentor Dr. Horga in his training in dopamine physiology, schizophrenia pathophysiology, and development as an independent investigator.

B. POSITIONS AND HONORS

Positions

1977-84	Medical School, St. Joseph University, Beirut, Lebanon
1985-89	Categorical Internship, Psychiatric Residency & Chief Residency, Univ. Tennessee, Memphis, TN
1989-91	Visiting Associate, NIMH, Clinical Brain Disorders Branch, Washington, DC
1991-92	Post Doctoral Fellow in Brain Imaging, Yale University
1992-96	Assistant Professor, Dept. of Psychiatry, Yale University
1994-96	Unit Chief, Neuropsychiatric Studies Unit, West Haven VAMC
1996-98	Assistant Professor, Dept. of Psychiatry, Columbia Univ. and NY State Psychiatric Institute
1998-03	Associate Professor, Clinical Psychiatry & Radiology, Columbia Univ. & NYS Psychiatric Institute
2003-	Professor of Clinical Psychiatry and Radiology, Columbia Univ. and NY
2005-2007	Chief, Division of Functional Brain Mapping
2007	Chief, Division of Translational Imaging
2007	Director of Clinical and Imaging Research, Leiber Center for Schizophrenia Research
2012	Associate Director of Columbia University PET Center

Honors

1993-94	NARSAD Young Investigator Award
1994	American College of Neuropsychopharmacology ACNP/Mead Johnson Award
1995	Yale University Chairman's Award
1997	Associate member, American College of Neuropsychopharmacology
1997-	NARSAD Young Investigator Award
1997-	Clinical Trials Award, Columbia University
	Irving Scholarship Award, Columbia University
2000-	NARSAD Independent Investigator Award
2000	Member, American College of Neuropsychopharmacology
2002	Gerald Klerman Honorable Mention Award by NARSAD for an outstanding Young Investigator
2004-2006	Member, Brain Imaging Council, Society of Nuclear Medicine
2007	Associate Editor, Neuropsychopharmacology
2008	NARSAD Distinguished Investigator Award
2009	President, Brain Imaging Council, Society of Nuclear Medicine

C. PEER-REVIEWED PUBLICATIONS (SELECTED FROM OVER 120).

1. Urban NB, Slifstein M, Thompson JL, Xu X, Girgis RR, Raheja S, Haney M, **Abi-Dargham A.**: Dopamine release in chronic cannabis users: a [¹¹C]raclopride Positron Emission Tomography study, *Biol Psychiatry*. 2012 Apr 15;71(8):677-83. doi: 10.1016/j.biopsych.2011.12.018. Epub 2012 Jan 29. **PMCID: PMC3314125**
2. Martinez D, Slifstein M, Gil R, Hwang DR, Huang Y, Perez A, Frankle WG, Laruelle M, Krystal J, **Abi-Dargham A.**, Positron emission tomography imaging of the serotonin transporter and 5-HT(1A) receptor in alcohol dependence. 2009 Jan 15;65(2):175-80 *Biol Psychiatry*. **PMCID: PMC2621104**
3. Schneier FR, **Abi-Dargham A.**, Martinez D, Slifstein M, Hwang DR, Liebowitz MR, Laruelle M.: Dopamine transporters, D(2) receptors, and dopamine release in generalized social anxiety disorder. *Depress Anxiety*. 2009 Jan 29. 2009;26(5):411-8. **PMCID: PMC2679094**
4. Kegeles LS, Slifstein M, Frankle WG, Xu X, Hackett E, Bae SA, Gonzales R, Kim JH, Alvarez B, Gil R, Laruelle M, **A. Abi-Dargham**: Dose-Occupancy Study of Striatal and Extrastriatal Dopamine D(2) Receptors by Aripiprazole in Schizophrenia with PET and [(18)F]Fallypride, *Neuropsychopharmacology*. 2008 Dec;33(13):3111-25
5. Martinez D, Slifstein M, Narendran R, Foltin RW, Broft A, Hwang DR, Perez A, **Abi-Dargham A.**, Fischman MW, Kleber HD, Laruelle M.: Dopamine D1 Receptors in Cocaine Dependence Measured with PET and the Choice to Self-Administer Cocaine. *Neuropsychopharmacology*. 2009 Jun;34(7):1774-82. **PMCID: PMC2680918**
6. N B. Urban, R R. Girgis, P Talbot, L S. Kegeles, X Xu, W. G Frankle, M Slifstein, **Abi-Dargham A.**, M Laruelle: Sustained recreational use of ecstasy is associated with altered pre and postsynaptic markers of serotonin transmission in neocortical areas: a PET study with [¹¹C]DASB and [¹¹C]MDL 100907, *Neuropsychopharmacology*, 2012, 37(6):1465-73, **PMCID: PMC3327851**
7. **Abi-Dargham A.**, Guo N, Narendran R, Hwang D, Ekelund J, Guillen O, Martinez D, Frankle G, Laruelle M: prefrontal dopamine transmission in schizophrenia: is d1 receptor a relevant biomarker? *Behav Pharmacol.*, 2005, Sept. 16 Suppl 1:S13.
8. **Anissa Abi-Dargham, M.D.**, Larry Kegeles, MD, PhD, Y. Zea-Ponce PhD , Osama Mawlawi, Ph.D., D. Martinez,, Marc Laruelle, MD and Larry Siever M.D.: Dopamine Transmission in Schizotypal Personality Disorder studied with SPECT [¹²³I]IBZM, *Biol Psychiatry*. 2004 May 15;55(10):1001-6
9. **A Abi-Dargham**, J. Rodenhiser, D. Printz, R. Gil, Y. Zea-Ponce, L. Kegeles, R. Weiss, T. Cooper, J. J. Mann, R. Van Heertum, J. Gorman, M. Laruelle, Evidence for increased activity of dopaminergic neurons in schizophrenia, *PNAS*, 2000, 97: 8104-8109.
10. L.S. Kegeles, **A. Abi-Dargham**, Y. Zea-Ponce, J. Rodenhiser, J. J. Mann, R. L. Van Heertum, T. B. Cooper, A. Carlsson and M. Laruelle: Modulation of Amphetamine-Induced Striatal Dopamine Release by Ketamine in Humans: Implications for Schizophrenia, *Biol. Psych.*, 2000, 48:627-640.
11. **Abi-Dargham**, L. Kegeles, D. Martinez, R. Innis, M. Laruelle, Dopamine mediation of positive reinforcing effects of amphetamine in stimulant naïve healthy volunteers: results from a large cohort. *Eur Neuropsychopharmacol.* 2003;13(6):459-68.
12. Diana Martinez, Roberto Gil, Mark Slifstein, Dah-Ren Hwang, Yiyun Huang, Audrey Perez, Lawrence Kegeles, Suzette Evans, John Krystal, Marc Laruelle **and Anissa Abi-Dargham**: Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum, *Biol Psych.*, 2005; 58(10):779-86.
13. W. Gordon Frankle, Rajesh Narendran, Yiyun Huang, Dah-Ren Hwang, Ilise Lombardo, Claudine Cangiano, Roberto Gil, Marc Laruelle **and Anissa Abi-Dargham**: Serotonin Transporter Availability in Patients with Schizophrenia: A Positron Emission Tomography Imaging Study with [¹¹C]DASB, *Biol Psych*, 2005, 57 (12) 1510: 6
14. M. Slifstein, L.S. Kegeles, R. Gonzales, W.G. Frankle, X. Xu, M. Laruelle, **A. Abi-Dargham**: [¹¹C]NNC 112 selectivity for dopamine D1 and serotonin 5-HT2A receptors: a PET study in healthy human subjects, 2007;27(10):1733-41.
15. Martinez, Hwang, Mawlawi, Slifstein, Kent, Simpson, Parsey, Hashimoto, Huang, Shinn, Van Heertum, **Abi-Dargham**, Caltabiano, Malizia, Cowley, Mann, Laruelle: Differential Occupancy of somatodendritic and postsynaptic 5-HT1A receptors by pindolol: a dose occupancy study with [¹¹C]WAY-100635 and Positron Emission Tomography in humans, *Neuropsychopharmacology*, 2001, 24:209.229.

D. RESEARCH SUPPORT

1 P50 MH086404-01 NIMH	Abi-Dargham	7/1/10-6/31/15
Title: Dopamine Dysfunction in Schizophrenia The major goal of this Center is to combine clinical imaging with PET and epigenetic and transgenic animal models to test the hypothesis that striatal dopamine hyperactivity during development leads to prefrontal cortical dopamine dysfunction in schizophrenia.		
Role: Center PI; Administrative Core: PI; Project 1: Prefrontal Dopamine Function in Schizophrenia		
1 K02 DA026075-06 NIDA	Abi-Dargham	7/1/09-6/30/14
Title: Cortical and striatal dopamine dysfunction in addiction and schizophrenia The candidate proposes to integrate PET and fMRI to explore the comorbidity between schizophrenia and substance abuse.		
Role: PI		
R01 DA022455-01A1 NIDA	Abi-Dargham	1yr no cost extension
Title: Imaging dopamine transmission in cannabis dependence The major goal is to assess indices of dopamine transmission in cannabis dependent subjects.		
Role: PI		
P50 AA-012870-11 NIAAA	Krystal	7/15/11 - 5/31/2016
Subcontract with Yale University Title: "Center for the Translational Neuroscience of Alcoholism" PET striatal dopamine release deficits with family history of alcoholism (PI: Anissa Abi-Dargham, M.D.) This project will examine dopamine transmission in at risk subjects for alcoholism.		
Role: Project Principal Investigator		
1 R01 MH63875-05A2 NIMH	Siever	8/1/08-7/31/13
Title: 5-HTT and 5HT2A Recetors in Impulsive Aggression and Effects of Fluoxetine The goal of this study is to assess serotonergic function in subjects with impulsivity and aggression.		
Role: Co-Investigator		
U01 MH076544 NIMH	Lieberman	1yr no cost extension
Title: Pharmacologic and Clinical Testing of a D1 Agonist for Neuropsychiatric Disorders The goal of this study is to measure the effects of a D1 agonist on cognition in schizophrenia.		
Role: Research Psychiatrist		
Distinguished Investigator Award Abi-Dargham 1yr no cost extension 1/1/09 – 12/31/13		
NARSAD Title: [18 F] DOPA imaging in prodromal schizophrenia: a biomarker for conversion The major goal of this project is to assess dopamine release in cannabis dependent patients with schizophrenia with a particular model to explain a negative interactivity between the two conditions.		
Role: PI		

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Daniel C. Javitt	POSITION TITLE Professor, Psychiatry and Neuroscience		
eRA COMMONS USER NAME JAVITD01			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Princeton University, Princeton, NJ Albert Einstein College of Medicine, NY Albert Einstein College of Medicine, NY	BA MD PhD	1979 1983 1990	Biology Medicine Neuroscience

A. Personal Statement

My research examines the functional and pharmacological properties of sensory and cognitive systems in human patients with schizophrenia and animal models of this disorder with techniques ranging from neurophysiology to functional neuroimaging. In his career development award, Dr. Guillermo Horga proposes a training plan that will give him a conceptual foundation and research experience in sensory learning systems that are disrupted in schizophrenia, a disruption that may lead to auditory hallucinations. I believe that Dr. Horga has the potential and has secured the resources to succeed in this endeavor, and I have considerable expertise to provide him with breadth and depth of training in these areas. The proposed work is of substantive interest to me, as it will speak to the neural mechanisms that lead to specific psychotic symptoms. Identification of this mechanistic link will be of high importance to the field.

B. Positions and Honors**Positions:**

- 1983-1984 Intern, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY
- 1984-1987 Resident, Department Of Psychiatry, AECOM
- 1987-1990 Fellow in Biological Psychiatry, Department of Psychiatry, AECOM
- 1990-1995 Assistant Professor, Department of Psychiatry, Albert Einstein College of Medicine
- 1995 – 2001 Associate professor, Dept. of Psychiatry, New York University School of Medicine
- 1995-present Director, Schizophrenia Research Division, Nathan Kline Institute, Orangeburg, NY
- 2001-2011 Professor, Dept. of Psychiatry and Neuroscience, New York University School of Medicine, New York, NY
- 2011-present Professor, Dept of Psychiatry and Neuroscience, Director, Division of Experimental Therapeutics, Columbia University College of Physicians and Surgeons, New York, NY

Honors (2001 – Present, Selected)

- 2001: Joel Elkes Research Award, American College of Neuropsychopharmacology, San Juan, PR
- 2003: MERIT Award, NIMH
- 2003: Fellow, ACNP
- 2007: Alexander Gralnick Award, Child Welfare League of America
- 2010 Co-chair, Institute of Medicine meeting: *Glutamate-related biomarkers in drug development for disorders of the nervous system*
- 2011 Member, Scientific advisory board, Brain Behavior Research Foundation (NARSAD)
- 2012 Stanley Dean Award, American College of Psychiatry

Committee membership:

- 1998 – 2002: CPP/BBBP-5 committee, NIH
- 2003 – 2009: BDCN-6/NPAS committee, NIH (Chair: 2007-2009)
- 2006-2007: Ad hoc member NIH CTSA review committee
- 2011: Chair, India-US Collaborative R21 review committee

C. Selected peer-reviewed publications (2009 – Present, from 240 total)

1. Butler PD, Abeles IY, Weiskopf NG, Tambini A, Jalbrzikowski M, Legatt ME, Zemon V, Loughead J, Gur RC, Javitt DC. Sensory contributions to impaired emotion processing in schizophrenia. *Schizophr Bull.* 2009;35:1095-107. PM#2762631
2. Javitt DC. Sensory processing in schizophrenia: neither simple nor intact. *Schizophr Bull.* 2009;35:1059-64. PM#2762632,
3. Javitt DC. When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annual rev clinical psychol* 2009;5:249-75.
4. Kantrowitz JT, Butler PD, Schechter I, Silipo G, Javitt DC. Seeing the world dimly: the impact of early visual deficits on visual experience in schizophrenia. *Schizophr Bull.* 2009;35:1085-94. PM#2762627,
5. Leitman DI, Laukka P, Juslin PN, Saccente E, Butler P, Javitt DC. Getting the cue: sensory contributions to auditory emotion recognition impairments in schizophrenia. *Schizophr Bull.* 2010;36:545-56. PM#2879690,
6. Leitman DI, Sehatpour P, Higgins BA, Foxe JJ, Silipo G, Javitt DC. Sensory deficits and distributed hierarchical dysfunction in schizophrenia. *Am J Psychiatry.* 2010;167:818-27.
7. Sehatpour P, Dias EC, Butler PD, Revheim N, Guilfoyle DN, Foxe JJ, Javitt DC. Impaired visual object processing across an occipital-frontal-hippocampal brain network in schizophrenia: an integrated neuroimaging study. *Arch Gen Psychiatry.* 2010;67:772-82.
8. Dias EC, Butler PD, Hoptman MJ, Javitt DC. Early sensory contributions to contextual encoding deficits in schizophrenia. *Arch Gen Psychiatry.* 2011;68:654-64.
9. Jacobson L, Javitt DC, Lavidor M. Activation of inhibition: diminishing impulsive behavior by direct current stimulation over the inferior frontal gyrus. *J Cogn Neurosci.* 2011;23:3380-7.
10. Javitt DC, Schoepp D, Kalivas PW, Volkow ND, Zarate C, Merchant K, Bear MF, Umbrecht D, Hajos M, Potter WZ, Lee CM. Translating glutamate: from pathophysiology to treatment. *Sci Transl Med.* 2011;3:102mr2.
11. Kantrowitz JT, Leitman DI, Lehrfeld JM, Laukka P, Juslin PN, Butler PD, Silipo G, Javitt DC. Reduction in Tonal Discriminations Predicts Receptive Emotion Processing Deficits in Schizophrenia and Schizoaffective Disorder. *Schizophr Bull.* 2011. Epub.
12. Martinez A, Hillyard SA, Bickel S, Dias EC, Butler PD, Javitt DC. Consequences of Magnocellular Dysfunction on Processing Attended Information in Schizophrenia. *Cereb Cortex.* 2011. epub
13. Chouake TL, Javitt DC, Lavidor M. Magnocellular training improves visual word recognition. *Front Hum Neurosci.* 2012;6 14.
14. Friedman T, Sehatpour P, Dias E, Perrin MJ, D.C. Differential relationships of mismatch negativity and visual P1 deficits to premorbid characteristics and functional outcome in schizophrenia *Biol Psychiatry.* 2012;in press.
15. Gold R, Butler PD, Revheim N, Leitman D, Hansen JA, Gur R, Kantrowitz JTL, P., Juslin JNS, G.S., Javitt DC. Auditory emotion recognition impairments in schizophrenia: Relationship to acoustic features and cognition. *Am J Psychiatry.* 2012.

C. Research Support (ongoing, last 3 years)

P50 MH086385 Javitt

7/23/09-6/30/14

NIMH

The Conte Center for Schizophrenia Research

The overall goal of this Conte Center is to develop new assessment and intervention approaches for schizophrenia based upon glutamatergic models and a focus on sensory function. A translational approach will be used including human and primate neurophysiological as well as postmortem/laser capture/gene array studies and efficacy of an NMDA agonist will be assessed.

Role P.I.

COMPLETED RESEARCH SUPPORT

R01 DA003383 Javitt

7/1/82-6/30/13

NIDA

Phencyclidine Abuse and Psychosis: Biomedical Mechanisms
Investigates mechanisms underlying PCP psychosis

Role: PI

R37 MH049334 Javitt	1/1/93 – 2/28/13 (MERITAward)
NIMH	
Early Cortical Processing in Schizophrenia	Uses event-related potentials to investigate mechanisms underlying cortical processing deficits in schizophrenia.
Role: PI	
U01 MH074356 Javitt	9/30/05-8/31/12
NIMH	
D-Serine Treatment of Schizophrenia	This project will consist of PK/PD, dose-finding and subsequent double-blind treatment studies at NKI involving patients with chronic schizophrenia, and investigating D-Serine effects on persistent negative symptoms and cognitive dysfunction.
Role: PI	
R24 MH082790 Javitt	5/24/08-3/31/12
NIMH	
Sensory Processing Dysfunction in Neuropsychiatric Illness	The overall goal of this project is the development of a network of collaborations that will encourage the systematic translations of basic behavioral theory, methods and findings into research designed to reduce the burden of mental illness behavioral disorders, particularly schizophrenia.
Role: PI	
P50 MH060450 Coyle	6/1/07-5/31/11
NIMH	
Biomarkers of NMDA dysfunction and D-Serine Effects.	This project consists of two components. First, neurocognitive measures will be added to a recently funded study of D-serine treatment in both chronic and prodromal subjects in order to evaluate the degree to which GMS agonist treatment can reverse or prevent neurocognitive deficits associated with schizophrenia. Second, parallel studies in transgenic mouse models will evaluate the degree to which ERP deficits in schizophrenia can be reproduced by genetic manipulations aimed at the NMDA GMS.
Role: Subcontract PI	
R21 MH075849 Martinez	4/15/07-3/31/11
NIMH	
Functional Brain Mapping in Schizophrenia	To systematically map visual processing areas magnocellular or Dorsal stream dysfunction in schizophrenia.
Role: Co-Investigator	
03T-483 Javitt (PI)	4/1/04-3/31/10
Stanley Foundation	
A Multi-Center controlled Clinical Trial of D-Serine vs. Placebo in patients with persistent negative and Cognitive Symptoms of Schizophrenia.	The goal of the study is to evaluate longer term effects of D-Serine, added to ongoing therapy, in the treatment of persistent negative and cognitive symptoms of schizophrenia.
Role: PI	
JAZZ Pharmaceuticals Javitt	12/11/07-1/31/10
Open Label, Pilot Study of adjunctive Xyrem for the treatment of schizophrenia and associated sleep disturbances	This is an open label, proof of concept pilot study to examine the effects of adjunctive Xyrem (sodium oxybate) in patients with schizophrenia and associated insomnia, looking at the effects of this medication on subjective sleep and sleep architecture, psychopathology and cognition.
Role: PI	
P50 MH066171 Lieberman (PI)	9/24/04-6/30/10
NIMH	

Neurobiology of Dopamine in Schizophrenia Prj. 4
To investigate the effectiveness of PCP on Monkeys evoked potentials.
Role: Subcontract PI

R01 MH066374 Butler (PI) 12/2/03-11/30/10

NIMH

Visual Processing in Schizophrenia

To investigate early visual processing dysfunction in schizophrenia

Role: Co-Investigator

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: **Delete Entry*** Start Date: * End Date: **Budget Period 1****A. Senior/Key Person**

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.	Guillermo		Horga		PD/PI	120,000.00	9.00			90,000.00	32,400.00	122,400.00
2.												
3.												
4.												
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6.												
7.												
8.												
9.	Total Funds requested for all Senior Key Persons in the attached file											

Total Senior/Key Person Additional Senior Key Persons: **Add Attachment****Delete Attachment****View Attachment****B. Other Personnel**

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	3.60		12,850.00	4,626.00	17,476.00	
1	Total Number Other Personnel						Total Other Personnel <input type="text" value="17,476.00"/>
	Total Salary, Wages and Fringe Benefits (A+B) <input type="text" value="139,876.00"/>						

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: **Delete Entry*** Start Date: * End Date: Budget Period 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment item	* Funds Requested (\$)
1.	
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10.	
11. Total funds requested for all equipment listed in the attached file	
	Total Equipment

Additional Equipment: **Add Attachment****Delete Attachment****View Attachment****D. Travel**

1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)
2. Foreign Travel Costs

Funds Requested (\$)**Total Travel Cost****E. Participant/Trainee Support Costs****Funds Requested (\$)**

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other

 Number of Participants/Trainees**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 1[Next Period](#)* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: [Delete Entry](#)Start Date: * End Date:

Budget Period 1

F. Other Direct Costs

1. Materials and Supplies
2. Publication Costs
3. Consultant Services
4. ADP/Computer Services
5. Subawards/Consortium/Contractual Costs
6. Equipment or Facility Rental/User Fees
7. Alterations and Renovations
8. 22,009.00
9.
10.

Funds Requested (\$)**Total Other Direct Costs** **G. Direct Costs****Funds Requested (\$)****Total Direct Costs (A thru F)** **H. Indirect Costs****Indirect Cost Type****Indirect Cost Rate (%)****Indirect Cost Base (\$)***** Funds Requested (\$)**

1. <input type="text" value="Modified TDC"/>	<input type="text" value="8.00"/>	<input type="text" value="172,400.00"/>	<input type="text" value="13,792.00"/>
2. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Total Indirect Costs Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs**Funds Requested (\$)****Total Direct and Indirect Institutional Costs (G + H)****J. Fee****Funds Requested (\$)**K. * Budget Justification [Add Attachment](#)[Delete Attachment](#)[View Attachment](#)

(Only attach one file.)

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

* ORGANIZATIONAL DUNS: 1672049940000

* Budget Type: Project Subaward/Consortium

Enter name of Organization: Research Foundation for Mental

Delete Entry

* Start Date: 04/01/2015

* End Date: 03/31/2016

Budget Period 2

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.	Guillermo		Horga		PD/PI	120,000.00	9.00			90,000.00	32,400.00	122,400.00
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8.												
9.	Total Funds requested for all Senior Key Persons in the attached file											

Total Senior/Key Person 122,400.00

Additional Senior Key Persons:

Add Attachment

Delete Attachment

View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)	
	Post Doctoral Associates							
	Graduate Students							
	Undergraduate Students							
	Secretarial/Clerical							
1	Research Assistant	3.60		13,235.00	4,765.00	18,000.00		
1	Total Number Other Personnel							
	Total Other Personnel						18,000.00	
	Total Salary, Wages and Fringe Benefits (A+B)							140,400.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: **Delete Entry*** Start Date: * End Date: Budget Period 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment item	* Funds Requested (\$)
1.	
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9.	
10.	
11. Total funds requested for all equipment listed in the attached file	
	Total Equipment

Additional Equipment: **Add Attachment****Delete Attachment****View Attachment****D. Travel**

1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)
2. Foreign Travel Costs

Funds Requested (\$)**Total Travel Cost****E. Participant/Trainee Support Costs****Funds Requested (\$)**

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other

Total Participant/Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 2[Next Period](#)* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: [Delete Entry](#)Start Date: * End Date:

Budget Period 2

F. Other Direct Costs

1. Materials and Supplies
2. Publication Costs
3. Consultant Services
4. ADP/Computer Services
5. Subawards/Consortium/Contractual Costs
6. Equipment or Facility Rental/User Fees
7. Alterations and Renovations
8. 22,523.00
9.
10.

Funds Requested (\$)**Total Other Direct Costs** **G. Direct Costs****Funds Requested (\$)****Total Direct Costs (A thru F)** **H. Indirect Costs****Indirect Cost Type****Indirect Cost Rate (%)****Indirect Cost Base (\$)***** Funds Requested (\$)**

1. <input type="text" value="Modified TDC"/>	<input type="text" value="8.00"/>	<input type="text" value="172,400.00"/>	<input type="text" value="13,792.00"/>
2. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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4. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Total Indirect Costs Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs**Funds Requested (\$)****Total Direct and Indirect Institutional Costs (G + H)****J. Fee****Funds Requested (\$)**K. * Budget Justification [Add Attachment](#)[Delete Attachment](#)[View Attachment](#)

(Only attach one file.)

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: **Delete Entry*** Start Date: * End Date: Budget Period 3**A. Senior/Key Person**

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.	Guillermo		Horga		PD/PI	120,000.00	9.00			90,000.00	32,400.00	122,400.00
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.	Total Funds requested for all Senior Key Persons in the attached file											<input type="text" value="122,400.00"/>

Total Senior/Key Person Additional Senior Key Persons: **Add Attachment****Delete Attachment****View Attachment****B. Other Personnel**

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	3.60		13,632.00	4,908.00	18,540.00	
1	Total Number Other Personnel						
	Total Other Personnel						
	Total Salary, Wages and Fringe Benefits (A+B)						

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: **Delete Entry*** Start Date: * End Date: Budget Period 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment item	* Funds Requested (\$)
1.	
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11. Total funds requested for all equipment listed in the attached file	
	Total Equipment

Additional Equipment: **Add Attachment****Delete Attachment****View Attachment****D. Travel**

1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)
2. Foreign Travel Costs

Funds Requested (\$)**Total Travel Cost****E. Participant/Trainee Support Costs**

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other

Funds Requested (\$)

<input type="text"/>

 Number of Participants/Trainees **Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 3[Next Period](#)* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: [Delete Entry](#)Start Date: * End Date:

Budget Period 3

F. Other Direct Costs

1. Materials and Supplies
2. Publication Costs
3. Consultant Services
4. ADP/Computer Services
5. Subawards/Consortium/Contractual Costs
6. Equipment or Facility Rental/User Fees
7. Alterations and Renovations
8. 22,954.00
9.
10.

Funds Requested (\$)**Total Other Direct Costs** **G. Direct Costs****Funds Requested (\$)****Total Direct Costs (A thru F)** **H. Indirect Costs****Indirect Cost Type****Indirect Cost Rate (%)****Indirect Cost Base (\$)***** Funds Requested (\$)**

1. <input type="text" value="Modified TDC"/>	<input type="text" value="8.00"/>	<input type="text" value="172,400.00"/>	<input type="text" value="13,792.00"/>
2. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Total Indirect Costs Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs**Funds Requested (\$)****Total Direct and Indirect Institutional Costs (G + H)****J. Fee****Funds Requested (\$)**K. * Budget Justification [Add Attachment](#)[Delete Attachment](#)[View Attachment](#)

(Only attach one file.)

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 4

* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: [Delete Entry](#)* Start Date: * End Date: Budget Period 4

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.	Guillermo		Horga		PD/PI	120,000.00	9.00			90,000.00	32,400.00	122,400.00
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.	Total Funds requested for all Senior Key Persons in the attached file											

Total Senior/Key Person Additional Senior Key Persons: [Add Attachment](#)[Delete Attachment](#)[View Attachment](#)

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	3.60		14,041.00	5,055.00	19,096.00	
1	Total Number Other Personnel						
	Total Other Personnel						<input type="text" value="19,096.00"/>
	Total Salary, Wages and Fringe Benefits (A+B)						
	<input type="text" value="141,496.00"/>						

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: **Delete Entry*** Start Date: * End Date: Budget Period 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment item	* Funds Requested (\$)
1.	
2.	
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10.	
11. Total funds requested for all equipment listed in the attached file	
	Total Equipment

Additional Equipment: **Add Attachment****Delete Attachment****View Attachment****D. Travel**

1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)
2. Foreign Travel Costs

Funds Requested (\$)**Total Travel Cost****E. Participant/Trainee Support Costs****Funds Requested (\$)**

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other

 Number of Participants/Trainees**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 4[Next Period](#)* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: [Delete Entry](#)Start Date: * End Date:

Budget Period 4

F. Other Direct Costs

1. Materials and Supplies
2. Publication Costs
3. Consultant Services
4. ADP/Computer Services
5. Subawards/Consortium/Contractual Costs
6. Equipment or Facility Rental/User Fees
7. Alterations and Renovations
8. 21,599.00
9.
10.

Funds Requested (\$)**Total Other Direct Costs** **G. Direct Costs****Funds Requested (\$)****Total Direct Costs (A thru F)** **H. Indirect Costs****Indirect Cost Type****Indirect Cost Rate (%)****Indirect Cost Base (\$)***** Funds Requested (\$)**

1. <input type="text" value="Modified TDC"/>	<input type="text" value="8.00"/>	<input type="text" value="172,399.00"/>	<input type="text" value="13,792.00"/>
2. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Total Indirect Costs Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs**Funds Requested (\$)****Total Direct and Indirect Institutional Costs (G + H)****J. Fee****Funds Requested (\$)**K. * Budget Justification [Add Attachment](#)[Delete Attachment](#)[View Attachment](#)

(Only attach one file.)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 5* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: **Delete Entry*** Start Date: * End Date: Budget Period 5**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment item	* Funds Requested (\$)
1. <input type="text"/>	<input type="text"/>
2. <input type="text"/>	<input type="text"/>
3. <input type="text"/>	<input type="text"/>
4. <input type="text"/>	<input type="text"/>
5. <input type="text"/>	<input type="text"/>
6. <input type="text"/>	<input type="text"/>
7. <input type="text"/>	<input type="text"/>
8. <input type="text"/>	<input type="text"/>
9. <input type="text"/>	<input type="text"/>
10. <input type="text"/>	<input type="text"/>
11. Total funds requested for all equipment listed in the attached file	<input type="text"/>
Total Equipment	<input type="text"/>

Additional Equipment: **Add Attachment****Delete Attachment****View Attachment****D. Travel**

1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost **E. Participant/Trainee Support Costs**

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other

Funds Requested (\$)**Number of Participants/Trainees** **Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 5* ORGANIZATIONAL DUNS: * Budget Type: Project Subaward/ConsortiumEnter name of Organization: **Delete Entry**Start Date: * End Date:

Budget Period 5

F. Other Direct Costs

1. Materials and Supplies
2. Publication Costs
3. Consultant Services
4. ADP/Computer Services
5. Subawards/Consortium/Contractual Costs
6. Equipment or Facility Rental/User Fees
7. Alterations and Renovations
8. 22,162.00
9.
10.

Funds Requested (\$)

<input type="text" value="4,168.00"/>
<input type="text"/>

Total Other Direct Costs **G. Direct Costs****Funds Requested (\$)****Total Direct Costs (A thru F)** **H. Indirect Costs****Indirect Cost Type****Indirect Cost Rate (%)****Indirect Cost Base (\$)***** Funds Requested (\$)**

1. <input type="text" value="Modified TDC"/>	<input type="text" value="8.00"/>	<input type="text" value="172,399.00"/>	<input type="text" value="13,792.00"/>
2. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Total Indirect Costs Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs**Funds Requested (\$)****Total Direct and Indirect Institutional Costs (G + H)****J. Fee****Funds Requested (\$)**

<input type="text"/>

K. * Budget Justification **Add Attachment****Delete Attachment****View Attachment**

(Only attach one file.)

BUDGET JUSTIFICATION

PERSONNEL: Fringe benefits are calculated at 36% of salaries for years 01-05, as per the **Research Foundation for Mental Hygiene's (RFMH)** approved rate.

Guillermo Horga, M.D., Principal Investigator (9.0 CM effort, salary support requested), is trained as a Psychiatrist and as a Post-Doctoral Research Fellow in Child and Adolescent Psychiatry in the Department of Psychiatry at Columbia University and The New York State Psychiatric Institute (Columbia / NYSPI). In June 2013, or upon receipt of the K-award (whichever is sooner), Dr. Horga will be appointed to Assistant Professor of Psychiatry in the Division of Child and Adolescent Psychiatry. Dr. Horga will devote 75% effort during years 01-05 of the K23 Mentored Research Career Development Award to the proposed training and research activities. He will be mentored by Dr. Peterson (primary mentor), Dr. Abi-Dargham (co-mentor), Dr. Javitt (co-mentor), and a panel of expert consultants. Dr. Horga will build on his basic skills in cognitive neuroscience, fMRI methods and psychiatry as he works towards the development of an independent program of research using neuroimaging methods to study the neural mechanisms of positive symptoms in schizophrenia as part of a broader long-term effort to extend our understanding of the pathophysiology of and improve treatment strategies for schizophrenia. Specific training goals for the 5-year period are (1) fMRI experimentation; (2) computational neuroscience; (3) cognition and perception research; (4) neurobiology and clinical aspects of psychotic disorders; and (5) responsible and ethical conduct in scientific research. During the award period, in addition to formal coursework, seminars, conferences, guided reading, and consultation with recognized experts, Dr. Horga will conduct mentored research designed to directly bridge these 5 training goals; specifically, he will conduct an fMRI study that aims to define the neural mechanisms underlying the generation of auditory hallucinations in schizophrenia. Supervised by Drs. Peterson, Abi-Dargham and Javitt, Dr. Horga will be responsible for management all aspects of his study, including design, data acquisition, imaging data management, and imaging data analysis. Throughout the award period, Dr. Horga will work towards reporting findings from this and related studies in conference presentations and first-authored manuscripts. During years 04-05 of the award period, Dr. Horga will prepare and submit an R01 proposal in which he will propose to link the neuroimaging of perceptual learning systems to clinical treatments and outcomes for schizophrenia.

MENTORS

Bradley S. Peterson, M.D., Primary Mentor Dr. Peterson is the Director of the Center for Pediatric Neuropsychiatry, former Director of the Division of Child and Adolescent Psychiatry, and former Director of MRI Research in the Department of Psychiatry at Columbia / NYSPI. He has devoted his career to the study of a wide range of neuropsychiatric disorders in children, particularly the mechanistic study of specific symptoms in Tourette syndrome and OCD with neuroimaging. As primary mentor on this K23 career development award, he will oversee the execution of all aspects of Dr. Horga's career development and research plans, including collaborations with other experts in neuroimaging and neuroscience. In weekly meetings, Dr. Peterson will closely supervise Dr. Horga's training in neuroimaging methods, cognitive neuroscience and the responsible conduct of research.

Anissa Abi-Dargham, M.D., Co-Mentor Dr. Abi-Dargham is Director of the Translational Imaging Unit at the New York State Psychiatric Institute at Columbia University and has extensive experience in the pathophysiology of schizophrenia and molecular imaging of the dopaminergic system in humans. Dr. Abi-Dargham has been directly involved in the conception and initial interpretation of the preliminary data for this award. In monthly meetings, Dr. Abi-Dargham will supervise recruitment of patients and oversee all of Dr. Horga's work towards achieving goal 4 of the training plan—to develop expertise in the neurobiological bases and clinical aspects of psychosis.

Daniel Javitt, M.D., Ph.D., Co-Mentor Dr. Javitt is Director of the Division of Experimental Therapeutics at the NYSPI and an expert in applying electrophysiological and imaging techniques to the study of perception and the pathophysiology of schizophrenia. In monthly meetings, Dr. Javitt will contribute towards achieving goal 4

of the training plan progress, to supervise experimental aspects related to perception and therapeutic strategies for schizophrenia, to help design a clinical trial for hallucinations in schizophrenia (years 04-05, towards the preparation of an R01 grant application), and to contribute to the accurate interpretation and presentation of the results from this project.

BUDGET JUSTIFICATION / RESEARCH SUPPORT

PERSONNEL

Research Assistant: Christina Read, B.A., 3.60 CM and salary support years 1-5 is requested. Ms. Read will assist in the recruitment, screening, scheduling and characterization of healthy participants. Research assistant will also assist in data management, MRI scanning and fMRI data pre-processing for all participants. Participant characterization will involve administering diagnostic instruments. Data management will involve entering clinical data into a database under the supervision of the PI. Research assistant will be trained in procedures for assessment, MRI scanning, and fMRI data pre-processing and analysis under the supervision of Dr. Horga, Dr. Peterson and Dr. Wang.

CONSULTANT COSTS: None

EQUIPMENT: None

To avoid an excessive burden of equipment costs, Dr. Peterson has generously made the following available to this project: medical exam essentials (exam room and furniture, etc.) and the Brain Imaging Laboratory's workstations, computing network and computing support personnel. These resources will be used outside regular work hours, if necessary.

SUPPLIES

1. **Project related supplies** \$515 year 1, \$5,477 yr 2, \$4,506 yr 3, \$5,304 yr 4, and \$4,168 is requested yr 5 for study related supplies including laboratory supplies (urine pregnancy tests, urine cups and latex gloves), Data analysis supplies (cartridges, DVD discs), etc.
2. **Tuition and Course Materials:** \$3,000 is requested in years 1&2, \$2,900 in year 3, and \$1,000 in years 4 &5 to cover tuition, books and other course materials. These courses include Behavioral Neuroscience, Auditory Perception, Learning and the Brain, and Theoretical Neuroscience, these courses are required in order to meet career goals and objectives.
3. **Computing:** \$7000 is requested for year 1 only.
 - Hardware and software:
 - (1) A Dell Precision T7600 with a Tesla C1060 GPU and 2 TB hard drive and uninterrupted power supply is required for database management of fMRI data, processing and computer-intensive statistical and machine-learning analysis of data, operator spreadsheets, locators for scans, and computer programming. Both the PI and the RFMH research assistant will have access to this computer.
 - (2) A portable Lenovo ThinkPad is required by the PI for data analysis, data presentation, manuscript preparation, information sharing and other performing K23 related task during travel out of the office (conferences, meetings, seminars, classes, consultations, etc.), and while the office is used by the RA for participant assessments. (3) One time purchases of general computer software needed for system function (Windows, etc.), data presentation and manuscript preparation (Microsoft office suite, adobe creative suite, endnote, etc.) and those related to data analysis (Matlab, SPSS, SAS, etc.). (4) A high capacity (3 TB) RAID external hard drive is needed for neuroimaging data backup. Flash memory devices (e.g. thumb drives) are needed for data transfer and temporary storage.

TRAVEL

\$3,000 in year 1 and \$4,000 in years 2-5 is requested to attend relevant scientific meetings for presentation of research findings and for peer consultation. This includes the annual meetings of SfN, OHBM, SIRC, and SOBP, and travel to visit the laboratory of Dr. Fletcher.

PARTICIPANT AND RESEARCH COSTS AND OTHERS

- 1. MRI Scans:** We will obtain scans on 60 participants. Each scan will require 2 hour of time in the scanning suite at a cost of \$650 per hour. Total cost for the duration of the study is $\$1300/2\text{ hr} \times 60\text{ scans} = \$78,000$. This amount will be divided equally between years 1-5 with a 3% increase in continuing years as per Research Foundation policies.
- 2. Neuroradiological Readings:** Total cost for the duration of the study will be 60 scans at \$50 per reading = \$3,000. This amount will be divided equally between years 1-5 with a 3% increase in continuing years as per Research Foundation policies.
- 3. Subject Payment:** Participant will be compensated for participating in study assessments of MRI scanning. It is anticipated that a total of 60 persons will be studied involving clinical interviews. Each subject will be paid $\$120 \times 60\text{ subjects} = \7200 . This amount will be divided equally between years 1-5.
- 4. Subject Travel** Participants will be reimbursed for transportation costs to and from MRI visit, at an estimated rate of \$30 per visit. Total cost is $60 \times \$30.00 = \1800 . This Amount will be divided equally over the 5 years of the study.
- 5. PsychIT Services:** \$649/FTE is requested in Year 01 and at the published rate yrs 2-5 to cover IT support including maintenance, upgrading, and troubleshooting for three individual computers.
- 6. Professional Society Membership:** \$300 is requested for all years. These include the costs of annual membership fees in SfN and OHBM.

RESEARCH & RELATED BUDGET - Cumulative Budget

Totals (\$)	
Section A, Senior/Key Person	612,000.00
Section B, Other Personnel	92,782.00
Total Number Other Personnel	5
Total Salary, Wages and Fringe Benefits (A+B)	704,782.00
Section C, Equipment	
Section D, Travel	19,000.00
1. Domestic	19,000.00
2. Foreign	
Section E, Participant/Trainee Support Costs	
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other	
6. Number of Participants/Trainees	
Section F, Other Direct Costs	138,217.00
1. Materials and Supplies	26,970.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other 1	111,247.00
9. Other 2	
10. Other 3	
Section G, Direct Costs (A thru F)	861,999.00
Section H, Indirect Costs	68,960.00
Section I, Total Direct and Indirect Costs (G + H)	930,959.00
Section J, Fee	

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix: * First Name:
 Middle Name:
 * Last Name:
 Suffix:

2. Human Subjects

Clinical Trial? No Yes
 * Agency-Defined Phase III Clinical Trial? No Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix: * First Name:
 Middle Name:
 * Last Name:
 Suffix:
 * Phone Number: Fax Number:
 Email:

* Title:

* Street1:
 Street2:
 * City:
 County/Parish:
 * State:
 Province:
 * Country: * Zip / Postal Code:

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? No Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: <http://stemcells.nih.gov/research/registry/>. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

PHS 398 Checklist

OMB Number: 0925-0001

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

New Resubmission Renewal Continuation Revision

Federal Identifier:

2. Change of Investigator / Change of Institution Questions

Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

* First Name:

Middle Name:

* Last Name:

Suffix:

Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes No

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes No

4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

Yes No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount (\$)

*Source(s)

<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>

5. * Disclosure Permission Statement

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

Yes No

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001

1. Application Type:

From SF424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated here for your reference, as you attach the sections that are appropriate for this Career Development Award.

New Resubmission Renewal Continuation Revision

2. Career Development Award Attachments:

Please attach applicable sections, below.

Introduction (if applicable)

1. Introduction to Application <i>(for RESUBMISSION applications only)</i>	intro_ra.pdf	Add Attachment	Delete Attachment	View Attachment
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Candidate Information

2. Candidate's Background	rplan_cb.pdf	Add Attachment	Delete Attachment	View Attachment
3. Career Goals and Objectives	rplan_cg.pdf	Add Attachment	Delete Attachment	View Attachment
4. Career Development/Training Activities During Award Period	rplan_cd.pdf	Add Attachment	Delete Attachment	View Attachment
5. Training in the Responsible Conduct of Research	rplan_tr.pdf	Add Attachment	Delete Attachment	View Attachment
6. Mentoring Plan <i>(when applicable)</i>		Add Attachment	Delete Attachment	View Attachment

Statements of Support

7. Statements by Mentor, Co-Mentors, Consultants, Contributors <i>(as appropriate)</i>	rplan_con.pdf	Add Attachment	Delete Attachment	View Attachment
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Environment and Institutional Commitment to Candidate

8. Description of Institutional Environment	rplan_env.pdf	Add Attachment	Delete Attachment	View Attachment
9. Institutional Commitment to Candidate's Research Career Development	rplan_com.pdf	Add Attachment	Delete Attachment	View Attachment

Research Plan

10. Specific Aims	rplan_nar.pdf	Add Attachment	Delete Attachment	View Attachment
11. * Research Strategy	rplan_rs.pdf	Add Attachment	Delete Attachment	View Attachment
12. Inclusion Enrollment Report <i>(for RENEWAL applications only)</i>		Add Attachment	Delete Attachment	View Attachment
13. Progress Report Publication List <i>(for RENEWAL applications only)</i>		Add Attachment	Delete Attachment	View Attachment

Human Subject Sections

14. Protection of Human Subjects	rplan_hs.pdf	Add Attachment	Delete Attachment	View Attachment
15. Inclusion of Women and Minorities	Inclusion_Women_Upload.pdf	Add Attachment	Delete Attachment	View Attachment
16. Targeted/Planned Enrollment	Targetted_Enroll_Upload.pdf	Add Attachment	Delete Attachment	View Attachment
17. Inclusion of Children	Inclusion_Children_Upload.pdf	Add Attachment	Delete Attachment	View Attachment

PHS 398 Career Development Award Supplemental Form

2. Career Development Award Attachments (continued):

Other Research Plan Sections

18. Vertebrate Animals

	Add Attachment	Delete Attachment	View Attachment
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19. Select Agent Research

	Add Attachment	Delete Attachment	View Attachment
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20. Consortium/Contractual Arrangements

	Add Attachment	Delete Attachment	View Attachment
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21. Resource Sharing Plan(s)

	Add Attachment	Delete Attachment	View Attachment
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Appendix (if applicable)

22. Appendix

Add Attachments	Delete Attachments	View Attachments
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3. * Citizenship:

U.S. Citizen or noncitizen national

Permanent Resident of U.S. Pending

Permanent Resident of U.S.

(If a permanent resident of the U.S., a notarized statement must be provided by the time of award)

Non-U.S. Citizen with temporary U.S. visa

INTRODUCTION TO THE REVISED APPLICATION

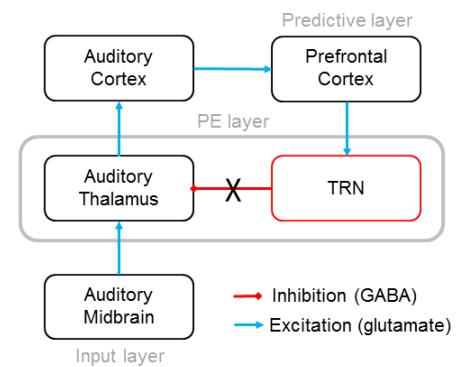
We thank the reviewers for their highly constructive, thorough review and their many favorable remarks. Enthusiasm for the application was “very high” despite “minor concerns.” Responses to critiques in each of the core criteria are summarized below. Corresponding changes in the application are indicated by a vertical line in the left margin (red, green, or blue in response to Reviewers R1, R2, or R3, respectively) and in maroon. The text box (right) contains the reviewers’ scores from the previous submission.

1 CAND.	2 CAR.	3 RES.	4 MENT.	5 ENV.
2	1	4	1	1
2	1	2	2	1
1	2	2	1	1

1. CANDIDATE: Deemed as an “outstanding” and “very promising” researcher who is “clearly devoted to patient-oriented research” and “at the ideal stage of his career to benefit from a K23.” No weaknesses were noted other than no extra-mural/federal funding (R2). Please note that part of my residency and my fellowship were supported by two extra-mural grants. Since I moved to the US (2009), I have also applied for a NARSAD YI award (pending), and since I received my green card (required for most federal grants) in Oct. 2012 I received an institutional K12 (May 2013). This K12 will support salary and training for 2 years but not a research project. If I receive the K23, I will decline the K12. Also note my two additional fMRI publications (Horga, et al., JCPP 2014; Marsh, Horga, et al. Biol Psychiatry 2013).

2. CAREER DEVELOPMENT PLAN: The reviewers noted that the “thoughtful”, “excellent” training plan “strikes a good balance.” R3 noted that the plan is somewhat ambitious but that “given the applicant’s history, and his letters, it seems like his energy and enthusiasm make this plan feasible”. I can reassure R3 that I am fully determined to complete and capitalize on my training plan, a plan that I strove to make demanding yet feasible.

3. RESEARCH PLAN: Deemed as “highly innovative” and “strongly hypothesis-driven” based on a “cutting-edge theoretical framework.” Reviewers highlighted its “direct translational value” and “careful consideration of possible confounding factors.” Because R1 noted that the task description and some related considerations (*description and proportion of stimuli, lack of control over AVHs, debriefing*) needed further clarification, the Task section has been substantially revised. *Group variance and Hypothesis 3.1:* Although new data shows the feasibility of testing Hypothesis 3.1 across all participants (Fig. 6c), I will also test it within the AVH group alone (see Hypothesis Testing, Aim 3). *Computational work:* I will develop a connectionist model with collaborators Drs. Maia and Miller to recapitulate the set of fMRI findings in AVH by a single deficit in a network comprising input, prediction error (PE), and predictive layers. My pilot implementation of this model (Fig.) was successful in simulating all the pilot findings in D1.4 (including hallucinations, defined by the number of silent periods during which auditory activation reaches a given threshold) via a disruption in inhibitory feedback within the PE layer. We placed this layer in the thalamus given previous reports of sensory PEs in the thalamus (ref. 9) and the role of GABAergic thalamic reticular neurons (TRN), thought to be dysfunctional in schizophrenia (Ferrarelli et al., Schizophr Bull 2011), in the generation of oddball responses in the auditory thalamus (Yu et al., Nat Neurosci 2009). Future simulations will include more detailed striato-thalamo-cortical anatomy and a spiking neuronal network with realistic receptors (following ref. 36) that will allow us to simulate responses to various treatments. **R2 & R3:** A new section, ‘Treatment Intervention section,’ describes *future plans for an intervention* that will be the aim of a subsequent R01 submission (and possibly an R21 in the interim). **R2 & R3** requested *details on success of capturing AVHs.* Briefly, we have successfully captured AVHs in the scanner in 9 out of 10 patients (20 AVH episodes on average; see Preliminary Data D1.4). *Plans for handling missing AVH data* were added to Hypothesis Testing, Aim 2. In response to R3, *claims regarding the project’s implications* are toned down throughout, particularly in Specific Aims and Significance. Nonetheless, the Treatment Intervention section specifies how the current project may guide the development of a novel treatment. Sample characteristics have been modified following R3’s comments about *IQ-matching* (no longer required) and the *binary classification of patients into AVH vs. non-AVH* (changed to a comparison of patients with high- vs. low-severity of AVH and a dimensional assessment of AVH severity across all patients) (see Sample); additional comments regarding *task design* and *critical tests related to AVH activations* are addressed in Task and Hypothesis Testing, Aim2.



4. MENTORS/CONSULTANTS/COLLABORATORS: All reviewers noted that the mentoring and consulting team is “top-notch”, “excellent”, and with an “impressive track record of mentoring.” R2 expressed the only concerns: (1) no publications with the co-mentors and (2) Dr. Peterson’s research focus on childhood psychiatric disorders rather than on schizophrenia. (1) Please note that I will start as Assistant Professor in Dr. Abi-Dargham’s division (Sept. 2013) and that we have co-authored a research poster (ACNP, 2012) and a manuscript currently under review in *Brain* (Horga, Schatz, Abi-Dargham and Peterson). Since Dr. Javitt’s recent move to NYSPI, we have applied for two NARSAD grants together to yoke the current fMRI paradigm to his ongoing clinical trial on hallucinations (Horga Bio and Javitt letter). (2) Please note that Dr. Peterson’s work is almost equally divided into adult and children populations, about a third of his work centers on method development (including fMRI methods for capturing transient symptoms such as tics, which are directly pertinent to capturing AVH), and that he has 10 imaging publications related to schizophrenia.

5. ENVIRONMENT: The environment was judged to be “first rank”, “excellent” and without weaknesses.

CAREER GOALS AND OBJECTIVES: SCIENTIFIC BIOGRAPHY

I am fully committed to an independent research career focused on the mechanistic understanding of psychotic disorders and their treatment, with the ultimate goal of improving patients' quality of life.

Early Interests

My captivation with the biological mechanisms of life began as early as high school. In particular, I was impressed by the sophistication of routine bodily functions such as oxygen transportation in the blood or food digestion. This initial interest was quickly transformed into burning curiosity about the biological underpinnings of the human *psyche* following my readings of Freud's *Psychopathology of Everyday Life* and *The Interpretation of Dreams*. Indeed, these books had a profound influence on my decision to study the biological mechanisms of thought. Even at this early stage, I recognized the importance of obtaining a *mechanistic* understanding of the brain.

Medical School

I entered medical school armed with my curiosity and my ambition to understand the workings of the human psyche. I was surprised to learn that psychiatry was treated as a discrete discipline from physiology or functional neuroanatomy, rarely taught from a neurobiological perspective. Despite this initial disappointment, or perhaps even driven by it, I persisted in my quest and eagerly read scientific journal articles and books about the neurobiology of mental processes and disorders in my spare time. Among these readings, I stumbled upon a paper in *Lancet* that left me completely fascinated by neuroimaging, as I saw the potential of this technique to study the mechanisms of psychiatric illness.

Residency Training

Residency in psychiatry at the Hospital Clinic of Barcelona gave me a unique opportunity to combine research and clinical training. From the beginning, I was most impressed by the phenomenology of schizophrenia. Witnessing first-hand a wide range of prototypical presentations of psychosis, I became convinced that psychotic symptoms must have distinct neurobiological origins. I became especially interested in the phenomenology of auditory verbal hallucinations in schizophrenia and, based on this experience, coauthored four book chapters on the clinical phenomenology and treatment of psychotic disorders.

Clinical Experience. During my training in psychiatry, I became aware of the many gaps in our knowledge on the mechanisms of disease and symptom generation. I could not give my patients satisfactory explanations for their unusual experiences or use objective measures to substantiate their diagnoses. These gaps in knowledge were particularly troubling in severe cases that required treatment with potentially fatal side effects (e.g., I published two case series on clozapine-induced epilepsy and electro-convulsive therapy in adolescents in the *Journal of Child and Adolescent Psychopharmacology*). My firm belief that research can fill these gaps and make a difference for the patient underlies my full commitment to a career in patient-oriented research.

Research/PhD program. In my second year of residency, I became involved with an ongoing functional imaging study in schizophrenia from which my PhD project stemmed. My work on this project culminated in several presentations at international meetings and two first-authored publications, one published in *Journal of Psychiatry and Neuroscience* and a second one currently under submission. In my fourth year of residency, I was awarded a scholarship from Astra-Zeneca that supported a research rotation in Dr. Monte Buchsbaum's laboratory at the Mount Sinai School of Medicine, NY. There, I took the lead on a study of the structural volume correlates of ventricular enlargement in schizophrenia (Horga et al., *European Archives of Psychiatry and Clinical Neuroscience* 2011). This experience taught me the value of interdisciplinary, collaborative work and the importance of having a deep understanding of all technical and conceptual aspects of one's research.

Postdoctoral Fellowship

After completing my residency in Spain, I was determined to see my training in neuroimaging through. Supported by a fellowship from the Alicia Koplowitz Foundation, I joined Dr. Brad Peterson's laboratory at the New York State Psychiatric Institute (NYSPI) at Columbia University, New York. The solid translational and technical components of this mentored fellowship provided me with an ideal platform for expanding my training in imaging methods and cognitive neuroscience. I acquired a fundamental understanding of functional magnetic resonance imaging (fMRI) techniques, and applied this knowledge to understanding the neural mechanisms of reinforcement learning (Horga et al., under external review in *Nature Neuroscience*) and contextual adaptation of cognitive control in both health (Horga et al., *Journal of Neuroscience* 2011) and illness, including prodromal schizophrenia, bulimia nervosa, major depression, and obsessive-compulsive disorder (Marsh, Horga et al., *American Journal of Psychiatry* 2011, with another two manuscripts under review, in *American Journal of Psychiatry* and in *PNAS*). This fruitful experience convinced me that fMRI is one

of the most promising tools available to yield a mechanistic understanding of psychiatric symptoms, including those associated with schizophrenia that had captured my interest early on. Therefore, in the last year of my fellowship, in collaboration with Drs. Peterson and Abi-Dargham at Columbia University, I designed an fMRI study of auditory verbal hallucinations in schizophrenia and collected preliminary data for this proposal.

Transition to an Independent Career

My ultimate career goal is to become an independent research scientist, conducting novel and therapeutically relevant research on psychotic disorders. In this moment of my career, I require support from a K23 career development award and additional training under the guidance of Drs. Peterson, Abi-Dargham, and Javitt at NYSPI to achieve this career goal. In particular, additional training at NYSPI will strengthen my knowledge of the experimental design, implementation, and advanced analysis of fMRI data, my primary training goal for this proposed award, through hands-on research experience, coursework, and intellectual interactions. During my residency in psychiatry and postdoctoral fellowship at Columbia University, I received exemplary instruction in clinical evaluation of psychotic disorders and familiarized myself with the analysis of functional neuroimaging data capturing psychological processes in health and illness. However, I have not yet mastered all of the skills necessary to independently conduct studies that utilize functional neuroimaging, and have never received formal training in advanced computational methods. Such techniques are crucial to my development as an independent researcher in the mechanistic study of psychotic disorders.

The proposed research program will enable me to acquire new knowledge and skills, including expertise in data analysis and programming using computational modeling and software packages such as Matlab and Emergent, and practical organizational and data management experience in conducting fMRI research. The ability to conduct fMRI experiments informed by computational models as an independent investigator is my immediate goal. I believe that training at NYSPI will help me realize this goal through, as attested by the impressive publication record and expertise of my mentors and collaborators. In addition to advancing my training in fMRI, another central part of the proposed training plan is to strengthen my understanding of cognitive, perception, and computational neuroscience. During my residency in psychiatry and my postdoctoral fellowship, my research mostly focused on psychiatric neuroimaging. The current proposal, which lies at the interface between auditory, cognitive, and computational neuroscience, will spur my growth in these new areas. Overall, receiving a K23 award will allow me to fully participate and benefit from the didactics and hands-on mentored experience necessary for the attainment of my ultimate goal of becoming a productive, NIH-funded, independent scientist.

CAREER DEVELOPMENT AND TRAINING ACTIVITIES DURING THE AWARD PERIOD

Rationale and Career Goals

My goal is to use this award to fully develop the skills needed to become an independent investigator focused on the application of computational neuroscience and fMRI to the mechanistic study of psychotic disorders. My educational goals for this award are centered on acquiring further knowledge and expertise in the following domains: (1) fMRI experimentation; (2) computational modeling; (3) cognition and perception research; (4) neurobiology and clinical assessment of psychotic disorders; and (5) responsible and ethical conduct in scientific research with vulnerable populations. My mentoring team, comprised of experts in clinical, experimental and computational neuroscience, is well suited to support my attainment of these goals.

Mentoring Team

Dr. Brad Peterson (*primary mentor*) is Suzanne Crosby Murphy Professor in Pediatric Neuropsychiatry and Director of MRI research at the Dept. of Psychiatry at the NYSPI. Dr. Peterson is an authority on the application of functional neuroimaging to the study of normal development and neuropsychiatric disorders across the lifespan. He has successfully mentored numerous K awardees and I am very fortunate to have developed a fruitful and invaluable relationship with him as my mentor. In our weekly meetings during the award period we will discuss all aspects of my training including methodological, design, and clinical issues related to my project.

Dr. Anissa Abi-Dargham (*co-mentor*) is Director of the Division of Translational Imaging at the NYSPI, Columbia University, and an expert in the pathophysiology of schizophrenia and molecular imaging of the dopaminergic system in humans. Dr. Abi-Dargham has been directly involved in the conception, recruitment and initial interpretation of my pilot work for this award. In our monthly meetings we will discuss my progress and review relevant work on the neurobiology of positive symptoms and schizophrenia.

Dr. Daniel Javitt (*co-mentor*) is Director of the Division of Experimental Therapeutics at the NYSPI, Columbia University, and an expert in applying electrophysiological techniques to the study of perception and the pathophysiology of schizophrenia. Dr. Javitt has already provided insightful feedback on the proposed research and we have begun to meet on a regular basis. In our monthly meetings, we will discuss my progress with a particular emphasis on experimental issues and the extant literature on perception in schizophrenia.

Progress Monitoring of the Program

My mentoring team will evaluate my progress annually to ensure compliance with the training and research goals. Evaluations will consider adherence to the proposed timeline, creativity and originality in data analysis, presentations at professional meetings, and number and quality of papers accepted in peer-reviewed journals. Dr. Peterson will be responsible for the oversight and coordination of the training plan. In addition, my three mentors will meet on a quarterly basis to discuss the progress of this award. Together with my external advisor/collaborator **Dr. Paul Fletcher**, an international expert on neuroimaging of learning in schizophrenia at the University of Cambridge, UK, with whom I will meet twice per year (in person or via videoconference), this **advisory committee** will ensure my successful research and training progress during the award period.

TRAINING GOALS

This application describes a comprehensive training program designed to help me launch a successful independent research career in the application of functional neuroimaging to the mechanistic study of psychosis. This training program encompasses formal coursework, guided readings, tutorials and discussions with renowned investigators, supervised research activities, and career development activities. The rationale and the specific training activities related to each of the five training domains are detailed below. **Table I** shows the proposed training timeline for the five-year award period.

TRAINING GOAL 1: To develop expertise in the design and implementation of fMRI experiments

Rationale. During my postdoctoral fellowship, I familiarized myself with fMRI image processing and analysis through coursework and practical experience. I also gained some initial experience in designing and conducting fMRI experiments. However, I need additional training in experimental design and in the execution of fMRI studies from beginning to end. In addition, to become a fully independent investigator conducting functional neuroimaging research, I need further training in advanced methods for data analysis.

Coursework

1. *Machine Learning* (W4771, Dept. of Computer Science; Instructor: Tony Jebara, PhD) provides an introduction to the field of machine learning (including classification techniques such as support vector machines) and hands-on experience in the application of machine-learning algorithms to fMRI data. These sophisticated tools have many applications to psychosis research including multivariate classification of patients into groups and mental states.
2. *Funding and Grantsmanship for Research and Career Development Activities* (M9780, Dept. of Medicine; Director: Jaime Rubin, PhD) is a short course that will provide me with the knowledge and skills required to obtain competitive grant support at the completion of the award period and throughout my career, including R01 grants.

Seminars and Conferences. I will attend seminars at the Brain Imaging Laboratory and at the Division of Translational Imaging at the NYSPI every other week, which cover advanced topics in experimental design, data collection and image analysis. I will also attend meetings of the *Society for Neuroscience* (SfN) annually and the *Organization of Human Brain Mapping* (OHBM) biannually for updates on advances in the neuroimaging field, where I will also present findings from the proposed research.

Tutorials.

1. *Analysis of fMRI Data and Computer Programming.* In monthly meetings with Dr. Zhishun Wang, Assistant Professor in the Dept. of Psychiatry, Columbia University, we will discuss practical issues in advanced fMRI analysis (including registration techniques, multivariate and Bayesian analysis) and computer programming with Matlab, and solidify the knowledge and skills required to conduct fMRI analysis independently.
2. *Advanced Applied Statistics.* In monthly meetings with Dr. Jun Liu, PhD, Statistician in the Dept. of Psychiatry, Columbia University, we will discuss pertinent topics in regression analysis as applied to fMRI and behavioral data (including mediation, regression diagnosis and model comparison). Through these meetings, I will gain expertise in the application of these techniques to clinical research. Dr. Liu will also supervise all statistical analyses for the proposed research.
3. *Participant Recruitment and Coordination of fMRI Projects.* In bimonthly meetings with Dr. Rachel Marsh, Assistant Professor in Psychiatry at Columbia University, New York and Director of Participant Recruitment at Dr. Peterson's lab, we will discuss specific practical issues related to the execution of fMRI research (including IRB approval, participant recruitment, and coordination of research assistants) and develop the managing skills required to conduct fMRI research independently.

TRAINING GOAL 2: To obtain advanced training in computational modeling

Rationale. Computational neuroscience utilizes unique tools for the *mechanistic* study of brain function. These tools are central to my research which aims to develop an explanatory model of brain dysfunction in psychosis. In particular, model-based fMRI (i.e., the analysis of neural activity related to variables derived from computational models) provides detailed insights into the mechanisms of brain functions that can afford a deeper level of understanding of psychotic disorders. During my postdoctoral fellowship, I applied computational modeling to the study of learning in health. However, I require further knowledge and expertise in the application of computational modeling to empirical studies of psychotic disorders. Goal 2 is designed to address these educational and training needs.

Coursework

1. *Learning and the Brain* (G4430, Dept. of Psychology; Instructor: Daphna Shohamy, PhD) covers the neural mechanisms that support learning, memory, and choice behavior with an emphasis on functional imaging and patient studies. This course will help me consolidate and extend my knowledge on mechanisms of learning as well as computational models of learning directly relevant to the current project and my proposed line of research.
2. *Theoretical Neuroscience* (G4360, Neurobiology & Behavior Program; Instructor: Larry Abbott, PhD) provides a comprehensive introduction to computational neuroscience, including mathematical techniques, computer simulation

methods, and modeling of neural systems function. This course will advance my knowledge in theoretical principles and specific techniques used in computational modeling.

Seminars and conferences. During the award period, I will attend the weekly *Neurotheory Seminar Series* at the Center for Theoretical Neuroscience at the NYSPI.

Tutorials

1. *Computational Modeling of Cognition and Learning.* I will meet with Dr. Tiago Maia, Adjunct Assistant Professor in the Dept. of Psychiatry, Columbia University, and expert on computational neuroscience and computational psychiatry, for 2 hours per month to discuss current topics in computational modeling and model-based analysis of fMRI data and behavior. Dr. Maia will also supervise my learning of the Emergent software and the development of a computational model of AVH that integrates the findings of the current project with the previous literature.
2. *Modeling of Neuronal Networks.* In regular meetings every other month with Dr. Ken Miller, Co-Director of the Center for Theoretical Neuroscience at Columbia University, I will obtain training in modeling of neuronal networks. Dr. Miller will also oversee the development of a biologically plausible model of such network dysfunction in hallucinations.

TRAINING GOAL 3: To acquire additional training in conducting perception and cognition research

Rationale. My proposed line of research in psychotic disorders focuses on the neural systems involved in perception and cognition, fields in which I have not had formal training. Thus, advancing my knowledge of basic and translational principles in perception and cognition neuroscience is central to my training and to the design and interpretation of my current and future research in this field.

Coursework

1. *Auditory Perception* (W3265, Dept. of Psychology; Instructor: Sarah Woolley, PhD) covers functional neuroanatomy of the auditory system and other topics related to the neuroscience of auditory processing and perception. This course will familiarize me with the basic mechanisms of perception, which is key to my study of perceptual auditory abnormalities in psychosis.
2. *Behavioral Neuroscience* (W2450, Dept. of Psychology, Instructor: Kathleen M Taylor, PhD) will provide an overview of the neural systems involved in emotion and cognition (from the principles governing neuronal activity to the relationship between brain activity and subjective experience).

Seminars and conferences. I will attend selected lectures and seminars related to perception and cognition at the NYSPI and the neighboring Neurological Institute, and participate in Dr. Schroeder's laboratory meetings and their monthly Journal Club (see Tutorials below). Attending the *Society for Neuroscience* annual meeting will also contribute to furthering my knowledge of perception and cognition research.

Tutorials.

1. *Auditory Cognition and Neuroscience.* In our monthly meetings at the NYSPI, Dr. Charles Schroeder, Director of the Laboratory for Cognitive Neuroscience and Neuroimaging at the Nathan Kline Institute, NY, member of the Dept. of Psychiatry at Columbia University, and expert in human and non-human auditory neuroscience, will consult on experimental issues, my research findings, and discuss up-to-date readings in the auditory neuroscience literature to aid in the interpretation of my findings and the design of future studies on perceptual processes in schizophrenia.
2. *Cognitive and Perceptual Neuroscience.* In our quarterly meetings, Dr. Vincent Ferrara, Associate Professor of Neuroscience at Columbia University and an expert in cognitive/perceptual systems neuroscience with functional imaging and neurophysiology in non-human animals, will advise me on experimental design issues and relevant topics in cognitive neuroscience that link basic and human research in cognition. Dr. Ferrara will also provide feedback and guidance on the analysis plan and control conditions for my study as well as consult on interpretive issues.

TRAINING GOAL 4: To develop expertise in the neurobiological bases and clinical assessment of psychotic disorders

Rationale. Building on my formal training in the neurobiology of psychosis, and clinical training in the evaluation of patients with schizophrenia, Goal 4 aims to increase my understanding of basic research in psychosis and the inclusion and standardized assessment of schizophrenia patients with psychotic symptoms in imaging research. More specifically, this training goal aims to develop the specific skills needed to recruit, properly assess, and retain patients with schizophrenia in research studies.

Tutorials.

1. *Normal Functions of the Dopaminergic System and its Dysfunction in Schizophrenia.* In our monthly meetings, my co-mentor Dr. Anissa Abi-Dargham, and I will discuss the dopaminergic system and its relationship to schizophrenia. Dr. Abi-Dargham will lead guided readings and discussions about recent advances in basic research and in human imaging with molecular techniques. Importantly, Dr. Abi-Dargham will be instrumental in the execution of my project by supervising patient recruitment, in helping me develop a coherent model of hallucinations that reconciles my findings within the dopaminergic theory framework, and in the conception of future experiments to test the relationship between dopaminergic dysfunction and perceptual predictive deficits in schizophrenia.

2. *Glutamatergic Theories and Perception in Schizophrenia.* Dr. Dan Javitt, an international proponent of glutamatergic models of schizophrenia and my co-mentor for the current proposal, and I will meet monthly to discuss recent research on perception and glutamatergic deficits in schizophrenia. His contribution will be central to the development of viable experimental paradigms to study perception in schizophrenia and to testing the clinical efficacy of novel treatments for hallucinations targeting sensory processing.
3. *Standardized Assessment of Psychotic Symptoms.* During my monthly meetings with Dr. Joshua Kantrowitz, Director of the Lieber Schizophrenia Research Clinic at the NYSPI, I will receive practical training in the screening of potential research participants and use of standardized scales for symptom assessment. This training will enable me to independently recruit and evaluate participants with standardized scales and semi-structured interviews for research purposes.

Hands-on Practicum. Throughout the award period, my participation in the monthly research meetings of the Lieber Schizophrenia Research Clinic will increase my familiarity with neurobiological models of psychotic disorders through presentations by Columbia University and outside investigators. Additionally, I will also actively take part in the weekly clinical meetings of the Lieber Clinic, organized by Dr. Jeffrey Lieberman. In these meetings, clinical and research staff review patients seeking the opportunity to participate in research, discuss the progress of ongoing treatment protocols and issues relevant to the assessment of patients with schizophrenia, review case histories of inpatients and outpatients in the Clinic, and discuss methods for enhancing recruitment and retention of research participants. These activities in the Lieber Clinic will provide me with hands-on experience in the assessment, recruitment and retention of patients with schizophrenia in research protocols.

Conferences. My attendance at the biennial *Schizophrenia International Research Conference* and the annual *Biological Psychiatry* and *Society for Neuroscience* meetings will help me further my understanding of the neurobiology of psychotic disorders and gain exposure to clinical advances in schizophrenia research.

Table I. Training Timeline

■ Coursework ■ Seminars/Conferences ■ Tutorials ■ Productivity

Training goals [†]	Year 1	Year 2	Year 3	Year 4	Year 5
1. fMRI and Research Skills	Machine Learning			Funding and Grantsmanship	
	Bimonthly Seminars at Brain Imaging Lab and Division of Translational Imaging at NYSPI; OHBM Meeting (Summer)				
	Analysis of fMRI Data and Programming – Zhishun Wang, PhD – 1 h/month Advanced Applied Statistics – Jun Liu, PhD – 1 h/2 months Recruitment and Coordination of fMRI Projects – Rachel Marsh, PhD – 1 h/2 months				
2. Computational Modeling		Learning and the Brain	Theoretical Neuroscience		
	Weekly Neurotheory Seminar Series at Columbia University; SfN Meeting (Fall)				
3. Cognition and Perception	Computational Modeling of Cognition and Learning – Tiago Maia, PhD – 2 h/month Modeling of Neuronal Networks – Ken Miller, PhD – 1 h/2 months				
	Auditory Perception		Behavioral Neuroscience		
	Cognition and perception seminars at NYSPI; Monthly auditory neuroscience Journal Club				
4. Neurobiology and Assessment of Psychosis	Auditory Cognition and Neuroscience – Charles Schroeder, PhD – 1 h/month Cognitive and Perceptual Neuroscience – Vincent Ferrera, PhD – 1 h/3 months				
	Monthly Research meetings of the Lieber Clinic; Weekly Clinical meetings of the Lieber Clinic Biennial Schizophrenia International Research Conference (Spring); Biological Psychiatry Meeting (Spring)				
	Dopaminergic System and its Dysfunction in Schizophrenia – Anissa Abi-Dargham, MD – 1h/month Glutamatergic Theories and Perception in Schizophrenia – Dan Javitt, MD, PhD – 1 h/month Standardized Assessment of Psychotic Symptoms – Joshua Kantrowitz, MD – 1 h/month				
5. Ethics	NYSPI-IRB Symposium	Ethics and Psychiatry		Responsible Conduct	
	Ethics Seminar Series – 1 h/month				
	Mentorship and Supervision – Brad Peterson, MD – 1h/week				
Research Productivity	Method optimization and preliminary data analysis			Development of AVH computational model	
	Participant recruitment, fMRI data collection and processing Preliminary data interpretation and conference presentations				K final analyses/writing R design/submittion

[†] Note. The colored bars in the top row denote the proportion of time spent on each activity for each year.

TRAINING GOAL 5: To obtain additional training in responsible and ethical conduct of scientific research

Rationale. Ethical conduct is arguably the most important prerequisite for any type of research, particularly in research involving vulnerable populations such as psychiatric patients. I have had extensive training related to ethical issues in research (e.g., I have participated in several seminars within the Workshops on Research Ethics at Columbia University, specific postdoctoral fellow seminars on ethical issues, and have attended IRB committee meetings). During the award period, I will continue this training by attending ethics seminars and discussing practical issues in this critical area with my mentor and co-mentors.

Dr. Peterson and I will discuss practical issues in the ethical treatment of patients and research conduct in our weekly meetings. I will also discuss these aspects of my research with my co-mentor, Dr. Abi-Dargham, who has been a member of the NYSPI IRB for over a decade and has extensive experience in dealing with issues of informed consent, capacity evaluation and responsible practices with regard to patient assessment and monitoring, especially in vulnerable populations (e.g., schizophrenia). In addition, I will attend courses and seminars (indicated below), as well as review and follow the recommendations for ethical research as presented in (1) "Guidelines for Review of Misconduct in Science for the Health Sciences Campus," Columbia University, and (2) "On Being a Scientist" Committee Report on the Conduct of Science, National Academy of Science, along with other readings suggested by Dr. Peterson.

Coursework, Workshops and Seminars.

I will attend the monthly seminar *Responsible Conduct of Research and Related Policy Issues* (CU, G4010) at Columbia University. I will also attend the Annual Ethics Symposium, a day-long workshop directed by the Chair of the NYSPI-IRB, addressing special issues concerning the capacity to consent to research and guardianship. Finally, I will take the 6-week course *Ethics and Psychiatry* (Dept. of Psychiatry Residency Training Program at Columbia University), which addresses current ethical issues related specifically to psychiatry. These coursework and seminars will help me to conduct independent research responsibly and ethically.

Dear Colleagues:

It is with great pleasure that I write in strong and unqualified support for Dr. Guillermo Horga's application for a Mentored Patient-Oriented Research Career Development K23 Award. In the duration of his training so far, Guillermo has managed to distinguish himself as an extremely promising young researcher. He is a brilliant, detail-oriented, systematic, highly competent, creative, and hard-working researcher, as well as a consummate clinician, who has an unwavering commitment to advance our understanding of the causes of serious psychiatric disorders. These personal strengths have helped him build a well-rounded network of mentorship and peers who have supported his acquisition of skills and the conduct of his research. Guillermo has demonstrated unprecedented facility with all the necessary tools to succeed in the challenges of a career path in the neuroimaging of psychotic disorders. He is an adaptable seeker of innovation, a generous collaborator, an enthusiastic partner in scientific exchange, and ardent in his pursuit of his academic and career goals. I have no doubt that Guillermo will become a leading investigator in schizophrenia research, and I assure you that we at Columbia University are fully committed to supporting Guillermo's research career.

I began working with Guillermo in 2009, upon his completion of residency in psychiatry at the Hospital Clinic of Barcelona, Spain. His experience there was primarily clinical, with a special emphasis on phenomenology, pathophysiology, and management of psychiatric illness. Motivated by his strong interest and passion for understanding the neurobiology of schizophrenia and mood disorders, he studied neuroimaging methods and participated in several studies over the course of his residency – most of the work being carried out during his spare time. He sought a close collaboration with Prof. Eduard Vieta, director of the Bipolar Disorder Unit, and Dr. Miquel Bernardo, director of the Schizophrenia Clinic Program of his former hospital, relationships that fostered his interests in exploring the neurobiological overlap of affective and non-affective psychoses. He contributed significantly to the writing of a textbook on schizoaffective disorder, took the lead on a PET study of brain metabolism in schizophrenia, and published several articles related to ECT in adolescents with schizophrenia. During his last year of residency, he went on a research rotation with a scholarship grant to the Neuroscience PET laboratory directed by Dr. Monte Buchsbaum at Mount Sinai Hospital, NY. There he acquired detailed knowledge of neuroanatomy and cortico-subcortical connectivity in schizophrenia, and he learned several methods for structural image analysis. Demonstrating a remarkable ability to multi-task, during the last years of residency, he undertook a concurrent PhD program for which he is now finishing his dissertation on brain metabolic patterns related to auditory verbal hallucinations in schizophrenia. His work during his residency culminated in two first authorship manuscripts in the field of neuroimaging.

Dr. Horga came to my laboratory July of 2009 under the auspices of a highly competitive post-doctoral research fellowship. During his time in my laboratory, he has shown an impressive commitment to his training in functional neuroimaging. He shows an uncommon passion for learning. He has read voraciously and attended many classes and seminars that have improved his understanding of fMRI signal modelling and statistics. A specific example of Guillermo's valuable contributions to our research is his involvement in a study of cognitive control. He embraced the project fully and has spear-headed several important improvements to our analysis techniques for that project, which led to a first-author publication in the *Journal of Neuroscience* and a second-author publication in *American Journal of Psychiatry*, with another first-author manuscript currently under external review in *Nature Neuroscience*. He also has established working relationships with several scientists at Columbia, all of whom have assisted him in formulating a comprehensive training program. He has made central contributions to several ongoing projects, and he has already become an integral member in our fMRI team, gaining the respect and trust of his peers, faculty, and research assistants.

Guillermo has excelled in his training in MRI research in psychiatry. Neuroimaging research, especially in psychiatric populations, is complex and demanding. Too few individuals with sufficient understanding of the capabilities and limitations of these methods are applying them to the mechanistic study of symptom generation. Guillermo requires further training in this complicated and highly technical field. With the resources, mentorship and collaborators that we secured, Guillermo is perfectly positioned for this unique K23 award.

I have extensive background in neuroimaging research that includes all four MRI modalities, the entire developmental spectrum, and many psychiatric disorders, leading to the publication of more than 200 peer-reviewed scientific articles. I have significant experience as a supervisor and mentor. I have mentored more than a dozen junior faculty members and over 30 postdoctoral fellows over the course of my career, many of whom have received K awards and have successfully gone on to become independent investigators. I have received various research and mentorship awards, including The Outstanding Mentor award from the American Academy of Child and Adolescent Psychiatry. I believe that I am qualified to continue to mentor Guillermo during his K award.

I am fully committed to guiding and promoting Guillermo's career development. The program of training that Guillermo, his co-mentors Drs. Anissa Abi-Dargham and Daniel Javitt, and I have carefully developed together is laid out in his application. In brief, the proposed training program outlines goals in four areas: (1) fMRI experiments, (2) computational neuroscience, (3) cognition and perception research, and (4) neurobiology and phenomenology of psychotic disorders. It is based on structured didactics, mentorship, tutorials, clinical research experience, laboratory visits, attendance

of national meetings, and supervised research. Drs. Abi-Dargham and Javitt will personally supervise his training in neurobiology of psychosis, and I will personally undertake to meet with Guillermo on a weekly basis, and to supervise his training in cognitive neuroscience and fMRI methods. In addition, I will oversee the coordination and ensure the completion of each specific goal of the training plan. Guillermo has put together an impressive team of mentors and collaborators that will foster his training and inform his work as a K23 awardee in vital ways. I have existing established collaborative relationships with these colleagues. I will solicit quarterly feedback from each mentor and collaborator. In addition, I will hold telephone (or in person when possible) mentor conferences with Drs. Abi-Dargham and Javitt to discuss Guillermo's progress. I will also synthesize this feedback and convey it to Guillermo in person every three months. Finally, I will provide Guillermo with annual written feedback that represents his progress towards his training, research and academic goals, which we will also discuss in person. I believe that this training program is both feasible and appropriate for filling the gaps of his knowledge base that will be needed for applying neuroimaging methods to the study of psychosis.

I am committed to ensuring the successful completion of Guillermo's proposed research project. Our laboratory, division, department and institution have well-established and proven infrastructure for the successful development of young investigators to independence and ample room for them to grow in new directions. As Director of the Brain Imaging Laboratory, I assure that our personnel, equipment and other resources will continue to be available for Guillermo's research and training needs. He is an integrated member of our group and participates in all our regular meetings and activities. As detailed in the training plan, faculty members in my group will continue to collaborate intimately with Guillermo in all aspects of his research and training. Guillermo will have fully sufficient access to our 3-Tesla scanner to complete his proposed study. I foresee no obstacles to Guillermo's achieving the aims of his proposal and goals of his training plan.

Guillermo has demonstrated great foresight, aptitude and unwavering commitment and determination along his path to establish himself as a neuroimager focused on the mechanisms of psychotic disorders. His project, entitled "Neural mechanisms of sensory predictions in schizophrenia with hallucinations," is both timely and important to the fields of schizophrenia and psychiatry in general. As an exceptional young investigator who has initiated the application of a growing skill set to contribute to our understanding of the neurobiology and psychopathology of psychosis, I have no doubt that Guillermo is ideally suited to carry out the K23 award: to successfully complete his research proposal and evolve into an independent translational investigator in psychosis. Equally, this K23 program arrives at the most appropriate moment in Guillermo's career development.

I am fully committed to Guillermo's training and promotion as well as to the mission of this K23. This is an ideal confluence of candidate, training and research plans, mentorship, and funding program. I enthusiastically and without qualifications endorse Guillermo's application and look forward with great pleasure to guiding and promoting his work on the proposed study and his continued career development.

Sincerely,



Bradley S. Peterson, M.D., Center for Pediatric Neuropsychiatry
Suzanne Crosby Murphy Professor in Pediatric Neuropsychiatry
Columbia College of Physicians & Surgeons and New York State Psychiatric Institute

Dear Guillermo,

DANIEL C. JAVITT, M.D., PH.D
Director, Division of Experimental Therapeutics
Professor of Psychiatry and Neuroscience

 COLUMBIA UNIVERSITY
College of Physicians
and Surgeons

EXPERIMENTAL THERAPEUTICS
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I will be delighted to serve as a co-mentor on your K23 Career Development Award entitled "Neural mechanisms of sensory predictions in schizophrenia with hallucinations." I feel that this Award will assist you greatly in becoming an accomplished researcher in the field of functional neuroimaging and cognitive neuroscience in schizophrenia.

I am impressed by several aspects of your proposal. First, you have initiated highly fruitful collaborations with Bradley Peterson's neuroimaging laboratory and Anissa Abi-Dargham's translational imaging laboratory, the Lieber Schizophrenia Research Clinic at Columbia University Medical Center, and Washington Heights Community Service. These working relationships will permit you to pursue work that is innovative both in terms of investigating symptomatic patients with schizophrenia and second in terms of utilizing sophisticated functional imaging techniques for the analysis of sensory predictive systems in this population. I feel that your proposal to link functional mechanisms underlying sensory predictions with auditory hallucinations and their neural signature is meritorious and will substantially further the limited literature regarding the role of perception (and neural processes in general) in the generation of psychotic symptoms. I am aware that you have recruited and scanned several patients with hallucinations already, which adds significantly to the feasibility of the project.

I am Director of the Division of Experimental Therapeutics at the New York Psychiatric Institute (Columbia University Medical Center), Director of the Silvio O. Conte Center for Schizophrenia Research, and Director of the Cognitive Neuroscience and Schizophrenia Research Program at the Nathan S. Kline Institute for Psychiatric Research. As you know, my research focuses on sensory processing deficits, NMDA dysfunction, and structure/function relationships in schizophrenia. I am particularly interested in the cognitive deficits that plague patients with schizophrenia as well as in their early sensory deficits and have studied this illness using rodent models, electrophysiology and pharmacological characterization.

During the time of the Award, our regular monthly meetings will teach you how we can use tools such as electrophysiology and receptor characterization to help inform and expand imaging research in humans with schizophrenia with the ultimate goal of understanding the pathophysiology of this disorder as well as the contribution of alterations in the glutamatergic system. This aspect is highly relevant to your proposal because it will equip you, as an imager, with a more in depth understanding of neuronal processes and it will provide a more solid base for your future translational and therapeutic studies, and the development of a computational model of hallucinations.

Under my mentorship, you will also strengthen your knowledge of clinical trial designs and I will assist you in the development of a therapeutic study on hallucinations towards the last phase of the award period. In particular, our treatment study of transcranial direct current stimulation in chronic hallucinators will provide an excellent foundation for your study and a practical source for patient recruitment. This and other ongoing studies with a focus on perception will additionally give you an opportunity to have first-hand exposure to issues related to perception research applied to schizophrenia.

I will closely coordinate this part of the career development plan with your primary mentor Dr. Brad Peterson. Also, Drs. Peterson and Abi-Dargham and I will have joint meetings over the phone or in person every 6 months to discuss your progress.

I am very pleased to be part of your mentoring team for the entire duration of this project. I will continue to meet with you regularly to discuss scientific and training aspects of this K23 as well as to further your knowledge of schizophrenia. I have successfully mentored numerous postdoctoral fellows and early faculty, many of whom have transitioned to independently funded careers. Therefore, I believe that I am qualified to help you achieve the training and research goals outlined in your application.

I believe that you are an ideal candidate for the K23 Award and I give you my unqualified support for this application.

Sincerely yours,

Daniel Javitt

Daniel C. Javitt, M.D., Ph.D.

Co-mentor statement

Dear Colleagues:

I am writing this letter with great enthusiasm to indicate my commitment to serve as a co-mentor on Dr. Guillermo Horga's K-23 application, "Neural mechanisms of sensory predictions in schizophrenia with hallucinations." I am Professor of Clinical Psychiatry, Director of the Division of Translational Imaging at the New York State Psychiatric Institute (NYSPI), Columbia University Medical Center, and Associate Director of the Columbia PET Center. Over the past year, I have gotten to know Dr. Horga and his work through his initiative to establish a collaboration with my laboratory and my close and ongoing relationships with his research mentors Drs. Peterson and Javitt and his collaborators.

Dr. Horga has demonstrated an unparalleled aptitude for neuroimaging research during his fellowship at Columbia University, where he has worked with Drs. Peterson, Wang, and other colleagues at New York State Psychiatric Institute, on the neural mechanisms of behavioral adaptations to conflict in healthy people (Horga et al., 2011 *J Neurosci*; Horga and Maia, 2012 *Front Hum Neurosci*) as well as in psychiatric populations (Marsh, Horga, et al., 2011 *Am J Psychiatry*). The honors that Dr. Horga has received for this work are well deserved. His work tackles critical aspects of human cognition because it brings central insights into the underlying mechanisms of goal-directed behavior and cognitive control, centrally relevant to many psychiatric disorders including schizophrenia. Dr. Horga's work during his residency is similarly impressive. In particular, his study comparing acute patients with schizophrenia with and without auditory hallucinations (Horga et al., *J Psychiatry Neurosci*) demonstrates a careful clinical design and a sophisticated statistical analysis and is particularly significant to the schizophrenia literature as it was the first study in hallucinations that included solely antipsychotic-naïve patients, thereby eliminating all possible treatment confounds. In the project outlined in his application, Dr. Horga aims to use advanced neuroimaging techniques to explore the neural mechanisms of sensory learning that produce hallucinatory experiences in patients with schizophrenia. The predictive-coding framework that he proposes is particularly interesting because it could explain not only hallucinations and other positive symptoms but possibly other symptom dimensions of schizophrenia. Also, his use of hallucinations as a model for psychosis makes it feasible to study both dysfunctional mechanisms and symptom-related activations within the same group of patients, a pre-requisite for the study of the



COLUMBIA UNIVERSITY

College of Physicians
and Surgeons

DEPARTMENT OF PSYCHIATRY

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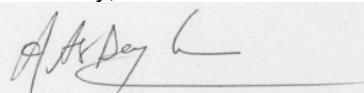
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mechanisms underlying symptom generation. By examining the mechanisms of psychotic symptoms in this manner, Dr. Horga's proposal is exactly where neuroimaging research into schizophrenia should be moving. His proposal employs a very sophisticated approach and his background in clinical psychiatry and fMRI research makes him an ideal candidate to carry out this important work.

My mentoring of Dr. Horga will take several forms and the principal goal of our meetings will be for Dr. Horga to become an expert in the pathophysiology and molecular mechanisms of schizophrenia with particular emphasis in the dopaminergic system. I will meet individually with Dr. Horga once per month throughout the award period. During these meetings, I will provide support and supervision for the recruitment procedures involved in his project, help expand his knowledge of the pathophysiology of schizophrenia through guided readings and discussions, and aid in the interpretation and analysis of data gathered in his proposed study. I will also be a consultant in Dr. Horga's development of a computational model of hallucinations that includes the dopaminergic and other main neurotransmitter systems. As the project advances, a focus of our discussions will become the development of a R01 proposal as this is a critical goal for Dr. Horga's career as an independent investigator in patient-oriented research.

Dr. Horga will have my continued support throughout this award. He will also be fully supported by the Division of Translational Imaging and the entire Department of Psychiatry. Dr. Horga is a very promising young investigator and we are very confident that he will make important contributions to the field of schizophrenia.

Sincerely,



Anissa Abi-Dargham, M.D., Professor of Clinical Psychiatry
Director, Division of Translational Imaging
Associate Director, Columbia PET Center

Columbia University Medical Center

Dear Guillermo,

I am very happy to serve as a collaborator on your K23 Career Development Award. Your study aims to investigate the mechanisms underlying sensory prediction-error signaling and their relationship to hallucinations in schizophrenia. I think this is a terrific project and I am delighted to be a part of it. In my role as a collaborator, I will be available to meet with you in person on a regular basis throughout the award period. The goal of our work together will be to help you learn the techniques necessary to study perception and cognition and to discuss relevant literature and neuroscientific approaches to study cognition and perception in humans and non-human animals. I will also give you critical feedback on your preliminary results and methods of analysis, and will help you design control experiments to refine the interpretation of your findings. Your career development and training thus far have well prepared you for this award. You are the type of exceptional young scientist for which the K-Award program was intended and I have no doubt that this award will launch your career as an independent researcher.

Sincerely,



Vincent Ferrera, Ph.D., Associate Professor of Neuroscience, Columbia University

Dear Guillermo,

I am very pleased to offer my support on your K23 Award proposal. I believe that your proposal to study sensory-learning mechanisms in patients with schizophrenia and auditory verbal hallucinations presents a wonderful opportunity to add to the scientific knowledge base about the neurobiology of schizophrenia. With the superb resources available to you at Columbia, including our support from the Lieber Schizophrenia Research Clinic in recruiting patients for your study, I am very confident that you will be successful in conducting this important study. As we have discussed, in our regular meetings we will discuss the phenomenology and diagnosis of the patients enrolled in your study. I will also supervise your formal training in the use of standardized scales for symptom assessment in schizophrenia. As part of your career development training, we will also discuss the techniques for recruitment and retention of patients with schizophrenia. I look forward to consulting with you on this exciting project and will do all I can to assist in your career development.

Sincerely,

Joshua Kantrowitz, MD

Director, Lieber Schizophrenia Research Clinic

Dear Guillermo,

I am delighted to serve as a collaborator on your K23 Career Development Award. Your proposal to use model-based fMRI to investigate the abnormalities in sensory mechanisms that underlie hallucinations in schizophrenia is of tremendous interest and promise. To help you with this project, I will work with you at the NYSPI to expand your knowledge in computational neuroscience and the application of computational models to the analysis of empirical data, particularly fMRI data. Specifically, we will focus on

the application of a computational model of predictive coding to analyze sensory predictive signals in healthy participants and patients with schizophrenia and auditory hallucinations in the patients. I will supervise and contribute to the development of a computational model of hallucinations that will aim at reconciling the findings from this study and the previous literature into a biologically plausible model able to explain auditory hallucinations from multiple causes. This model will incorporate different neurotransmitter systems and will have enough neurobiological detail to simulate responses to different pharmacological agents, thus informing treatment development. Since your arrival at Columbia University, we have had a very fruitful and enriching collaboration. I have truly enjoyed our working together on several manuscripts, two of which are already published, with a third one currently under external review at *Nature Neuroscience*. I strongly support your plans to become an independent investigator, as I am keenly aware of all that you have to offer to the field. I will work closely with you throughout the award period both on your current study and in developing future studies. By combining your clinical background with the exceptional training in computational neuroscience and functional neuroimaging that you will have the opportunity to receive here at Columbia University, you will be well prepared to become a leader in the study of the mechanisms and treatment of schizophrenia and psychotic disorders. Your application brings together an exceptional candidate and an exciting study. I am therefore delighted to be a part of this project.

Sincerely,
Tiago V. Maia, Ph.D.



Adjunct Assistant Professor, Department of Psychiatry, NYSPI & Columbia College of Physicians and Surgeons

Dear Guillermo,

I am very pleased to collaborate with you on your K23 Award research project and its corresponding training plan. I am co-director of the Center for Theoretical Neuroscience at Columbia University. My area of expertise is the use of theoretical and computational methods to unravel the circuitry of the cerebral cortex, the rules by which this circuitry develops and learns, and the computational functions of this circuitry. Your project presents a very interesting problem regarding the predictive mechanisms that may be involved in abnormal perceptions in schizophrenia. With our expertise in theoretical neuroscience and modeling neuronal networks in sensory systems, our group and I will help you further your knowledge in computational methods and their practical implementation. As part of your training, I look forward to your participating in the graduate course Theoretical Neuroscience (G4360), which my colleagues from the Center for Theoretical Neuroscience and I teach at Columbia University. This course will provide you with a comprehensive introduction to computational neuroscience and applied computer simulation methods that will be particularly useful for your development of a computational model of hallucinations based on predictive coding. In addition, as you describe in your K23 application, we will meet periodically to discuss the progress of your project and I or members of our group will supervise the development of your model of hallucinations, with an emphasis on simulations at the level of neural circuits. You have the full support of myself and our group for your outstanding application.

Sincerely,
Kenneth D. Miller, Ph.D.,
Professor and Vice-Chair, Dept. of Neuroscience; Co-Director, Center for Theoretical Neuroscience, Columbia University



Dear Guillermo,

I am delighted to commit my support to your application for a K23 Award. As director of a research group in Neuroscience and Psychiatry, and a member of the Department of Psychiatry at Columbia, I am keenly interested in collaborating with you and promoting your efforts to apply the methods of cognitive and auditory neuroscience to the study of psychotic disorders. My work focuses on the neuronal mechanisms of sensory and cognitive processes both at the level of neural systems and at the level of single neurons. While my studies are mainly focused on normal functioning, my work also investigates specific mechanistic models and hypotheses concerning neural dysfunction in schizophrenia, some of which are directly relevant for your application. Your proposal of studying prediction-error signals in the auditory cortex with sparse-sampling fMRI and their relationship to auditory hallucinations is very exciting and dovetails very well with my research interests. I believe that the project that you have outlined is important to the field of Schizophrenia Research and I am excited about helping you in carrying this through to completion. I also think that with your expertise and track records in functional MRI, psychiatry, and schizophrenia, you are superbly qualified to conduct such research.

As collaborator I will be able to contribute my own expertise to training you further in designing and carrying out an experiment in auditory neuroscience that will test relevant questions about the neural bases of abnormal perception in schizophrenia. I will help you interpret the complex data that will result from your investigations from a basic research perspective and suggest ways in which that data will answer the questions that you ask. In our regular monthly meetings, I will work with you towards achieving your training goal of advancing your knowledge in auditory neuroscience through guided readings and discussions on experimental issues as well as recent findings relevant to the auditory perception and cognition.

As we discussed, your attendance of my laboratory meetings at the Columbia and regular participation in our Journal Club, will be critical to building and maintaining your in-depth understanding in auditory research in human and nonhuman primates, and will allow your work to be informed by and contribute to, our ongoing projects. I believe that you are in exactly the right place in your career to benefit most from a mentored career development award. In fact, based on your previous work and your productivity, I think you are an ideal candidate for the award. I have no doubt that you will be very successful in your career, and I look forward to continuing my part in your development as a physician and scientist.

Sincerely,



Charles E. Schroeder, Ph.D. Professor, Department of Psychiatry, Columbia University College of Physicians and Surgeons

Dear Guillermo,

I am delighted to offer my support for your application for a K23 Award. I will meet with you regularly at the NYSPI throughout the term of the grant to train you in techniques for fMRI data analysis. I will meet with you individually on a monthly basis and provide you with detailed, hands-on instruction in applying statistical models and programming in Matlab to fMRI data. We will focus our work together on helping you master these techniques and on applying them to the data that you will collect for your K award on the mechanisms of auditory hallucinations in schizophrenia. I have great regard for you as a scientist and colleague, and I am confident that you are precisely the kind of candidate for whom this award is meant. I look forward to working with you closely on your research.

Sincerely yours,

Zhishun Wang, Ph.D., Assistant Professor, Department of Psychiatry, Columbia University

Dear Guillermo,

I am extremely pleased to support your K23 Award application. I happily agree to continue working with you on expanding your knowledge of biostatistics and its application to fMRI data. Throughout the award period, I will meet with you on a bimonthly basis to provide you with instruction on developing and applying statistical models and diagnostics to the data that you collect from your exciting study of hallucinations. I know that you are an excellent candidate for this award.

Sincerely,

Jun Liu, Ph.D., Assistant Professor, Department of Psychiatry, Columbia University

Dear Guillermo,

I am very eager to collaborate on your K23 proposal. I am an Assistant Professor of Psychology in Psychiatry and a faculty member of the Brain Imaging Laboratory at the NYSPI. I have extensive experience training members of the Brain Imaging Laboratory in the administration of clinical research instruments to participants of our neuroimaging studies. I have also directed participant recruitment and coordinated research assistants over the past six years. In our regular meetings, I will continue to guide you in your execution of fMRI experiments involving psychiatric populations, and will supervise your training in the recruitment of study participants and the successful coordination of the elegant project that you described. You are an incredible scientist and I look forward to our continued collaboration as you begin your independent career as an investigator of the highest caliber.

Sincerely,

Rachel Marsh, Ph.D., Assistant Professor of Clinical Psychology (in Psychiatry), Columbia University



Department of Psychiatry

Dear Guillermo,

I am honoured to serve as an advisor on your K23 Award proposal. Your proposal describes a timely and highly translational study that fits well the direction towards which our field of schizophrenia research is moving. Since my research in learning dysfunctions in schizophrenia is closely related to your proposal, my advice and critical feedback will, I hope, help you to meet your training and career goals. During the period of this Award, I will consult with you at least twice per year (or more frequently if needed) via videoconference and in person at international meetings. You are also welcome to visit my laboratory at the University of Cambridge at least twice during the award period, as we have discussed. I think that you will find our work on learning dysfunctions in schizophrenia and how they relate to delusions and other psychotic experiences highly relevant for your project. You have expressed interest in learning more about the 'Bayesian brain' and the role of different neurotransmitters in generating and updating predictions. During our interactions, I will provide guidance on your learning of these topics, as I believe that your knowledge in this area will be central to the development of a computational model of hallucinations. I will provide written updates to your primary mentor Dr. Bradley Peterson after our conversations in order to identify areas of knowledge that require additional training.

I believe that you are an ideal candidate for a K23 career development award and that your project, with help from this award and your outstanding mentoring team, will contribute to the advancement of the field of psychosis research.

Yours sincerely,

Paul Fletcher MB BS MRCPsych PhD, FMedSci
Bernard Wolfe Professor of Health Neuroscience
Wellcome Trust Senior Research Fellow in Clinical Science
Hon. Consultant Psychiatrist

DESCRIPTION OF INSTITUTIONAL ENVIRONMENT

The Research Foundation for Mental Hygiene Inc, sponsors the award for this application if funded.

FACILITIES AND OTHER RESOURCES

ENVIRONMENT – Contribution to success

Dr. Horga and his research team are supported by significant clinical research and imaging resources in the Department of Psychiatry at Columbia University and the New York State Psychiatric Institute (CU/NYSPI). Its resources, research faculty and staff, combined with those of the Research Foundation for Mental Hygiene, have made the Department of Psychiatry at CU/NYSPI one of the nation's most respected psychiatric research centers with long-standing experience in conducting clinical research studies. **The facilities and other resources available to this investigative team include everything needed to undertake and complete the proposed project successfully.** They have research space that is contiguous and extends from the ground level (the MRI suite) to two floors above within the same building where the PI (Dr. Horga) and his co-investigators have offices down the hall from the image processing laboratory and next to the Lieber Schizophrenia Research Clinic. This ensures easy access to resources, communication, and provides the foundation for this research team to grow and expand their collaborative work. The support from the Lieber Schizophrenia Research Clinic in the CU/NYPSI Department of Psychiatry, the Washington Heights Community Service, and the Division of Translational Imaging (directed by Dr. Abi-Dargham, co-mentor in this application) will ensure the successful recruitment of patients with schizophrenia for the proposed study. Additional referrals will come from other clinical resources within the CU/NYSPI Department of Psychiatry (described below), including the Division of Experimental Therapeutics (directed by Dr. Javitt, co-mentor in this application), which is conducting a clinical trial on schizophrenia with hallucinations and will be thus a useful resource for patient referrals. The intellectual environment in the Department of Psychiatry is rich with other extramurally funded investigators who are doing work that is complementary to the proposed project. These facilities provide a scientific environment that is supportive of the proposed research and success of the project.

INSTITUTIONAL COMMITMENT TO EARLY STAGE INVESTIGATORS

The PI qualifies as an Early Stage Investigator who has extensive evidence of institutional commitment to his development as an academic researcher. His 12-month academic appointment includes a total of 9.0 person months (75% effort) dedicated to research. He already has sufficient laboratory space and access to equipment for this project, as evidenced by his ability to yield the preliminary data for this first K23 application. His access to the clinical research resources described below is evidenced by his recruitment of 10 patients with frequent hallucinations to participate in his fMRI study on hallucinations (see Preliminary Data in Research Strategy-Approach). His access to the imaging resources in the Department of Psychiatry is also evidenced by these studies, as well as by his fMRI studies of healthy individuals, and patients with other psychiatric disorders (see Biosketch-Horga). These imaging data were acquired, processed and analyzed using the imaging resources of the Brain Imaging Laboratory (directed by Dr. Brad Peterson, primary mentor) and the MRI Unit. Please note that most of the researchers in the MRI Unit are affiliated with the Division of Translational Imaging, where Dr. Horga holds an appointment.



Research Foundation for Mental Hygiene, Inc.
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June 18, 2013

Dear Committee Members:

It is with great pleasure that we write this letter in support of Dr. Guillermo Horga's application for a K23 career development award. Dr. Horga is an outstanding and accomplished young investigator applying neuroscience approaches to the study of schizophrenia and psychotic disorders. On behalf of the New York State Psychiatric Institute and the Department of Psychiatry at Columbia University, we wholeheartedly offer our commitment to his development as a physician-scientist. Dr. Horga has been an involved and highly regarded member of our department as a post-doctoral research fellow in Child and Adolescent Psychiatry (2009-2012). He recently joined our faculty as an associate research scientist and is now being promoted to assistant professor.

We are very pleased that Dr. Horga is submitting his career development award proposal, "Neural mechanisms of sensory predictions in schizophrenia with auditory hallucinations" to the NIMH. During the award period, he will work on projects that complement and extend beyond those that he has been working on with Dr. Peterson. Dr. Horga and his mentoring team have prepared a comprehensive training plan through which he will develop expertise and gain experience in advanced fMRI techniques and research skills, computational-modeling approaches to neuroscience, experimental cognitive and perceptual neuroscience, neurobiology and assessment of psychiatric disorders, and responsible conduct of research. His training program includes structured didactics, private tutorials, and hands-on training that will primarily take place in our institution. To support the execution of his research and training plans, Dr. Horga has assembled an impressive team of mentors and collaborators, who are highly accomplished investigators in neuroscience and psychiatry. Dr. Horga's award is mentored by Drs. Bradley Peterson, Anissa Abi-Dargham and Daniel Jayitt, who have extensive experience in the successful mentoring of young investigators. Mentoring and supervision in the areas of computational modeling, cognitive neuroscience, fMRI methods and standardized assessment will also be provided by Drs. Vincent Ferrara, Tiago Maia, Ken Miller, Charles Schroeder, Joshua Kaitrowitz, Rachel Marsh, Zhishun Wang, and Jun Liu.

Our Department of Psychiatry has a longstanding track record of nurturing young faculty along the path to intellectual independence. We are fully committed to the retention, development, and successful advancement of Dr. Horga along this path. During the period of the K23 career development award, considerable institutional resources will be made available to Dr. Horga to enable him to realize his proposed project, train and gain the necessary expertise to succeed. The Division of Translational Imaging will provide office space, equipment and related resources. Dr. Horga will also have access to the facilities of the New York State Psychiatric Institute and Columbia University as outlined in his proposal, including the MRI Research Unit and the Center for Pediatric Neuropsychiatry. We will also provide Dr. Horga at least 75% of protected time to devote to the research and training activities outlined in his proposal. In August 2013, Dr. Horga will be appointed to the rank of *Assistant Professor of Clinical Psychiatry* in the Department of Psychiatry, which includes all rights and privileges pertaining to faculty status. The Department of Psychiatry may look to Dr. Horga provide a limited amount of teaching services, which will not exceed 25% of his time.

In summary, as an exceptional candidate for the K23 career development award, Dr. Horga has designed a training plan that promises to provide an unparalleled foundation in the application of fMRI techniques and computational modeling to the cognitive, perceptual neuroscience of schizophrenia and hallucinations and ultimately address challenges of treatment for patients with refractory psychotic symptoms. This unique and fitting award program will provide him with an invaluable opportunity to develop his important line of investigation and mature into an independent investigator. The Division of Translational Imaging, the Department of Psychiatry and the New York State Psychiatric Institute are in an excellent position to provide the necessary resources to ensure the successful completion of Dr. Horga's proposed research and training plans. We are very excited about his proposal and he has the full and unqualified support of our department and institution in this application.

Sincerely,

Janelle Greenhill, M.P.H.
Director of Administration

Jeffrey A. Lieberman, M.D.
Lieber Prof. of Psychiatry &
Lawrence C. Kolb Prof. of
Psychiatry & Department Chair

Anissa Abi-Dargham, M.D.
Translational Imaging
Division Chief

SPECIFIC AIMS

Active psychosis in schizophrenia is among the most severe and burdensome of medical conditions worldwide.¹ Schizophrenia research to date has succeeded in describing brain abnormalities in patients but has failed to clarify the mechanisms underlying hallucinations and other core psychotic symptoms of this disorder.² The overarching goal of this proposal is to define the neural mechanisms that generate these psychotic symptoms.

A fundamental function of the brain is to learn regularities in the environment and *predict* upcoming events and their contingencies (e.g., anticipating hearing a voice when answering the phone). Internal *predictions*, rather than passive responses to external cues, are increasingly recognized to drive activity in sensory systems and belief formation,³⁻⁹ which suggests that abnormal predictions may explain the abnormal percepts and beliefs typical of schizophrenia.¹⁰⁻¹¹ Disruptions in these *predictive mechanisms* of the brain, specifically in prediction-error signaling, correlate with delusion propensity¹² and have been recently hypothesized to underlie hallucinations.^{11,13} However, a causal link between predictive mechanisms and psychotic symptoms has yet to be established. Thus, the aim of this proposal is to define the neural correlates of auditory-verbal *predictions* (i.e., the expectation of hearing voices depending on varying probabilities of the occurrence of speech stimuli during a novel speech discrimination task) in healthy controls and patients who are actively hallucinating, and to establish a direct link between these auditory-verbal *predictions* and auditory-verbal *hallucinations* (i.e., the perception of voices without a corresponding stimulus, as indicated by patients in the scanner). I propose a hybrid experimental design that encompasses symptom-capturing and task-based methods and a novel approach that combines functional magnetic resonance (fMRI) and computational modeling. This “model-based fMRI” approach can provide insights into the mechanisms, beyond the mere mapping, of the neural process under study.¹⁴ I hypothesize that disruptions in predictive mechanisms underlie the generation of hallucinations in schizophrenia. Specifically, deficient prediction-error signaling may increase baseline activity in the auditory cortex,¹⁵⁻¹⁸ thereby inducing hallucinatory auditory percepts (**Fig. 2**).

This novel design and the application of model-based fMRI to the study of hallucinations will, for the first time, demonstrate a direct linkage of predictive mechanisms in the brain and the online experience of psychotic symptoms within the same experiment (**Fig. 2**).

Aim 1 To determine the neural correlates of auditory-verbal predictions and prediction errors in patients with schizophrenia (with and without hallucinations) and healthy controls.

Hypothesis 1.1 Activation in the auditory cortex in healthy controls will correlate strongly with auditory-verbal prediction errors (the difference between the predicted and the actual speech stimulus).

Hypothesis 1.2 The correlation between activation in the auditory cortex and auditory-verbal prediction errors will be weaker in patients than in controls, particularly in patients with hallucinations.

Aim 2 To map neural activations associated with auditory-verbal hallucinations in schizophrenia.

Hypothesis 2 Hallucination events will be associated with increased activity in the auditory cortex and limbic regions and decreased activity in the thalamus relative to non-hallucination, silent events.^{15,17-19}

Aim 3 To determine the relationship between auditory-verbal prediction errors and auditory-verbal hallucinations in schizophrenia.

Hypothesis 3.1 Participants with greater deficits in auditory-verbal prediction errors will have greater resting activity in the auditory cortex during silence, a neural phenotype of hallucinations.

Hypothesis 3.2 Manipulation of auditory-verbal predictions will diminish the occurrence of auditory-verbal hallucinations in patients.

The novel application of model-based fMRI will contribute to a mechanistic understanding of how specific dysfunctions in predictive mechanisms may lead to psychotic symptoms. This finding will help advance our understanding of schizophrenia and other neuropsychiatric disorders in which psychotic symptoms occur by linking a specific brain dysfunction to the occurrence of a specific psychotic symptom. This research may help identify novel therapeutic targets—auditory-verbal predictions and their neural correlates, which will be detailed in a new computational model of hallucinations. This research has the potential to inform treatment development and to identify brain phenotypes amenable to study in animal models. Under the auspices of this mentored award, I will develop expertise in imaging and computational methods that will directly contribute to the successful completion of this work and to my transition to an independent investigator focused on patient-oriented research on the pathophysiology and treatment of psychotic disorders.

RESEARCH STRATEGY

A Significance An emerging body of work relates abnormalities in predictive and learning mechanisms to psychotic symptoms. Specifically, the application of reinforcement-learning models to fMRI has identified abnormal prediction-error signaling during associative learning in schizophrenia^{20,21} that correlates with the severity of delusions¹², arguably some of this decade's most influential discoveries in psychosis research. These studies have provided in-depth insights into schizophrenia by capitalizing on detailed models of reinforcement learning. However, it is not yet known how predictive and learning mechanisms lead to symptom generation. The current proposal will use a novel approach that combines fMRI and computational modeling to help understand how abnormal predictive mechanisms in the auditory system lead to auditory verbal hallucinations (AVH) in schizophrenia. Thus, the main contribution of the proposed project will be to establish for the first time a direct link between abnormal predictive mechanisms and symptom generation within the same individuals. This contribution is significant because it will fill a gap in the schizophrenia literature regarding the mechanisms of symptom generation and has the potential to help define a novel target (sensory predictions) that is amenable to therapeutic modification (e.g., with learning-based, noninvasive approaches^{22,23}). By comparing patients with and without AVH, this project will also establish the specificity of sensory predictive deficits to AVH. The predictive deficits in the auditory system will likely be responsive to treatment and may thus provide an objective measure for monitoring treatment response. Importantly, sensory predictions themselves may arise as a viable target for learning-based therapeutic interventions, which could benefit the many patients that are unresponsive to conventional treatments.^{22,24}

B Background Hallucinations and other positive symptoms typically progress in parallel and are thus thought to share a common neural substrate. However, in contrast with other positive symptoms, AVHs consist of discrete events, lasting only a few seconds on average.²⁵ Thus, the neural mechanisms underlying AVH are more amenable to study within the duration of a standard experimental session and with techniques affording a suitable temporal resolution such as fMRI. Previous research has demonstrated increased activity in the auditory cortex during AVH.^{17,18} Since stimulation of the sensory cortex causes subjective percepts,²⁶ this increased activity of the auditory cortex in schizophrenia is thought to cause AVH percepts.²⁷ However, the mechanism underlying this increased activity in the auditory cortex remains unknown. Studies show that the normal dampening of auditory response to predictable speech is impaired in patients with AVH,²⁸ suggesting that a predictive deficit may lead to hallucinations, presumably by a failure to attenuate sensory activity.

The predictive-coding model of perception and inference postulates that neural networks involved in perception learn regularities in the external world, and signal deviations from these regularities.^{29,30} By generating an internal representation of the external world and continuously updating this representation based on experience, this predictive coding serves to minimize redundant information and noise from sensory inputs, generate beliefs about the causes of these inputs, and increase the efficiency of neural processing. This coding scheme is supported by a hierarchical architecture (Fig. 1) of message passing that consists of feedback connections that convey predictions from higher to lower levels and feed-forward connections that carry the errors—or differences—between the predicted input and the actual input (i.e., prediction errors). In sum, this model provides the basis for energy-saving, prediction-based attenuation of sensory activity.¹¹ Empirical research supports this model: (1) neurons in the sensory cortex encode prediction errors in behaving animals;^{4,5} (2) many neural networks share this model's architecture;²⁹ and (3) stimulus predictability has a robust effect on hemodynamic signals in human sensory cortices.^{6,9,31,32}

Predictive coding is especially appealing for explaining psychosis This model postulates that brain activity is mainly driven by internal predictions, not by external stimuli—that animals “smell what they expect, not what they sniff”.⁹ Activation of the sensory cortex induces percepts, so a faulty prediction-based attenuation of sensory activity may increase activity in the sensory cortex and thus induce percepts in the absence of actual external stimuli, thereby explaining hallucinations (Fig. 2). A disruption in this predictive coding scheme could also explain false Research Strategy

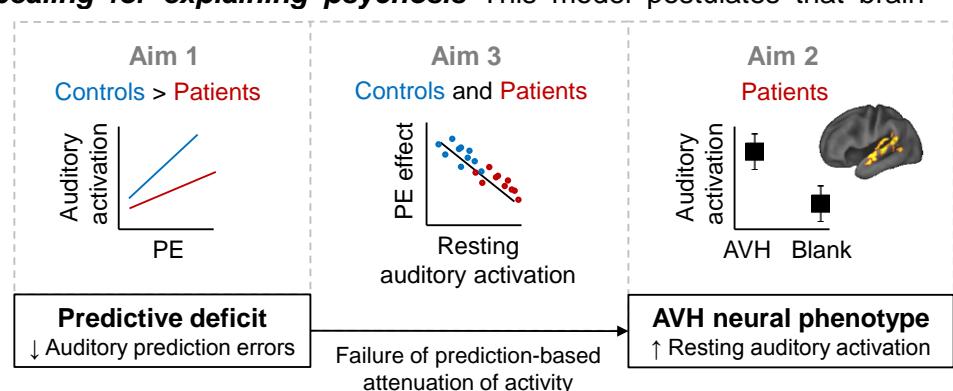
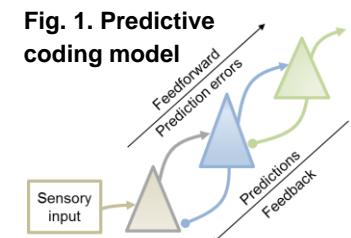


Fig. 2. Mechanistic model of AVH (bottom) and expected findings in line with the model (top), each corresponding to a specific aim. PE: Prediction error.

beliefs about the causes of these percepts²⁹ (i.e., *delusions*). In addition, abnormal predictive-coding mechanisms and inefficient use of energy may disrupt numerous other neural processes and account for *other symptom domains* (such as cognitive symptoms)³³ of schizophrenia. Thus, deficits in predictive coding have the potential to account for various symptom domains of schizophrenia. Although the predictive-coding framework has not yet been applied to schizophrenia research, longstanding neurophysiological findings can be reinterpreted within this framework to support predictive deficits in schizophrenia. Recent findings support that the mismatch negativity (MMN), an auditory event-related potential to deviant (unexpected or “oddball”) auditory stimuli, is best explained as an index of sensory prediction errors.³⁴⁻³⁶ Because *deficits in MMN and oddball effects* have been consistently reported in schizophrenia^{37,38} and correlate with AVH severity,³⁹ previous evidence supports our working hypothesis that **a deficit in sensory prediction errors underlies hallucinations** in schizophrenia (**Fig. 2**). The reliable structural abnormalities in the auditory cortex found in patients with schizophrenia in both *in vivo* imaging and post-mortem studies⁴⁰⁻⁴⁵ also support this putative sensory dysfunction.

C Innovation This study is innovative in at least 5 ways. (1) Because scanner noise induces activation in the auditory cortex that is difficult to distinguish from AVH-related activations, it may lower the sensitivity of conventional fMRI to detect AVH-related activations. The novel application of sparse-sampling or “silent” fMRI, which has become the standard in auditory fMRI research but has not been used in AVH research, will permit the dissociation of responses to scanner noise from responses to AVH and to external speech. (2) To facilitate direct comparisons between responses to AVH and to external speech, I will use a novel **speech database developed for this project**. This database codes for phenomenological features relevant in AVH⁴⁶ and will permit matching of speech stimuli to the features of subject-specific AVH experienced in the scanner. (3) Whereas most AVH studies use either symptom-capture or cognitive-task-based approaches, I propose a **hybrid design** that combines symptom-capturing and a mechanistic, perceptual-cognitive paradigm. (4) To minimize confounds related to intellectual and cognitive deficits in schizophrenia, I will use a speech discrimination task with **low cognitive demand**. (5) Lastly, I will use a computational model of predictive coding and **model-based fMRI** to identify, for the first time, the neural systems that implement predictions and prediction errors of speech and determine how their dysfunction may lead to AVH.

D Approach

D1 Preliminary Data This section describes (1) previous work on the neural correlates of AVH in schizophrenia, (2) previous work on predictive signals in adaptive control, (3) previous application of model-based fMRI, (4) pilot work on sensory prediction errors in AVH and health, and (5) evidence for the feasibility of the recruitment strategy.

1. Brain metabolism during hallucinations in schizophrenia

We conducted a fluorodeoxyglucose PET study comparing two matched groups of acute, antipsychotic-naïve, first-episode schizophrenia patients: one with AVH and the other without AVH. This study¹⁷ showed that activation along the superior temporal gyrus/sulcus, a voice-selective region of the auditory cortex in health,⁴⁷ is specifically increased during AVH (**Fig. 3**), without the confound of medications.

2. Predictive signals in the brain mediate contextual adaptation

In a study of the mechanisms underlying context-dependent adaptation to conflict in healthy participants, published in *Journal of Neuroscience*,⁴⁸ we describe a dorsomedial prefrontal system anticipatory, pre-stimulus activation to context, and interacts with a conflict-reactive system to produce context-dependent adaptations in behavior (**Fig. 4**). This work is evidence of my successful research on predictive mechanisms in cognition.

3. Model-based fMRI study of learning We studied normal neural functioning during learning. Using a reinforcement-learning algorithm, we identified value signals in an area of the putamen that strengthens its connections with the premotor cortex as individuals form stimulus-response associations (**Fig. 5**), consistent with computational models of learning. This study, currently under external review, demonstrates my ability to successfully apply computational models of reinforcement learning to fMRI and behavioral data.



Fig. 3. (a) Increased activity in AVH patients relative to non-AVH patients with schizophrenia. **(b)** Voice-selective regions of the auditory cortex in health.

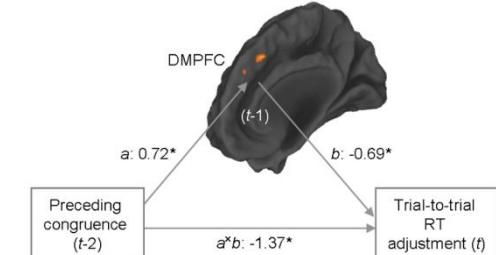


Fig. 4. Mediation of contextual adaptation in behavior by dorsal prefrontal cortex

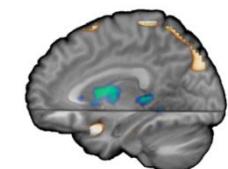


Fig. 5. Changes in putamen connectivity in learners versus nonlearners

4. Predictive coding in AVH and health Using the paradigm proposed in this application, we collected data for 10 patients with schizophrenia and frequent AVH and 10 socio-demographically matched controls. Owing to a careful clinical selection, we successfully captured AVH in the scanner: patients had on average 20 AVH episodes (according to the operationalization in 'Task' and confirmed by post-scanning debriefing) while controls had none. Nine out of 10 patients had AVH. Supporting Hypothesis 2, the left auditory cortex was more activated during AVH trials than during blank trials ($p < .05$, corrected; **Fig. 6a**); the thalamus and midbrain were less activated during AVH than during blank trials. Patients performed the task as accurately as controls (95% accuracy). We fitted a predictive-coding algorithm to estimate prediction errors of speech on a trial-by-trial basis (see Model-based Analysis). Each participant showed strong prediction-error signals in the auditory cortex (~30% of the BOLD signal variance). Importantly, and in support of Hypothesis 1.2, patients had significantly reduced prediction-error signals in the right auditory cortex compared with controls ($p < .05$, corrected; **Fig. 6b**). This prediction-error deficit correlated strongly with the magnitude of resting activation in auditory cortex across all participants ($r = -.9$, $p = 10^{-13}$; **Fig. 6c**), suggesting that the prediction-error deficit may account for the resting hyperactivity that underlies AVH (supporting Hypothesis 3.1). I will extend this work for the current proposal.

5. Feasibility of recruitment We are confident in meeting our recruitment target of 11 patients/year with collaboration from the Division of Translational Imaging (which recruits over 15 drug-free patients annually; see Recruitment). We will easily recruit over 7 controls/year with help from Dr. Peterson's laboratory.

D2 Research Plan Following the specific aims and hypothesis of the proposed study, I will acquire fMRI, behavioral, socio-demographic, clinical, and neuropsychological data from 3 different groups of participants: (1) patients with schizophrenia and **high-severity** AVH ($n=20$), (2) patients with schizophrenia and **low-severity** AVH ($n=20$), and (3) healthy controls ($n=20$). Years 1 through 3½ of the award period will be dedicated to data collection and concomitant processing of fMRI data to ensure its stability and quality. During years 3½ through 5, I will develop a computational model of AVH based on the findings from this and previous studies, complete all statistical analyses, interpret the study findings and report them for publication. Findings from the proposed study will allow me, in collaboration with my mentoring team, to develop a treatment for AVH that will target predictive mechanisms through feedback-based cognitive training. During year 5 I will begin to design a clinical trial testing this AVH treatment for a subsequent R grant application (see 'Treatment Intervention').

Sample The sample will consist of 60 participants, divided into 3 groups: (1) 20 drug-free patients with schizophrenia and **high-severity**, daily AVH (**high-AVH**), (2) 20 drug-free patients with schizophrenia and **low-severity** AVH (**low-AVH**), and (3) 20 healthy controls.

Inclusion criteria Patients will meet DSM-IV-TR criteria for schizophrenia or schizoaffective disorder. Patients will be referred from clinicians who follow them regularly and will be off of antipsychotic medication for at least 3 weeks (see below). A dimensional assessment of lifetime severity of AVH will be obtained in all patients based on the Lifetime Dimensions of Psychosis Scale (LDPS). **High-AVH patients** will meet the DSM-IV-TR criterion A2 *hallucinations*; they will report clearly hearing voices in the absence of corresponding external speech daily, several times per day, in the past two weeks, and have a lifetime history of severe, persistent AVH (LDPS severity and duration > 2). **Low-AVH patients** with infrequent, mild AVH will deny having experienced AVH in the past two months and will have no history of severe, persistent AVH (LDPS severity and duration ≤ 2). Additionally, all participants will be 18-55 year-old and fluent English-speakers.

Exclusion criteria for all participants will be any current drug use disorders, current major affective episodes, neurological disorders or hearing impairment. Healthy controls will not have any Axis-I psychiatric disorders.

Matching Patients and controls will be matched on socio-demographic characteristics (including age, sex, handedness and socioeconomic status of the family). In addition, the patients with **high- and low-AVH** will be matched on PANSS subscores other than P3 *hallucinatory behavior* and on previous antipsychotic exposure.

Medication (see Protection of Human Subjects for details) To minimize medication confounds, an effort will be made to only include patients who are maintained free of psychotropic drugs for a minimum of 3 weeks prior to participation in the study. These will be outpatients who are (1) already medication free or naïve or (2) are currently on medication but require a change due to ineffectiveness or intolerable side effects.

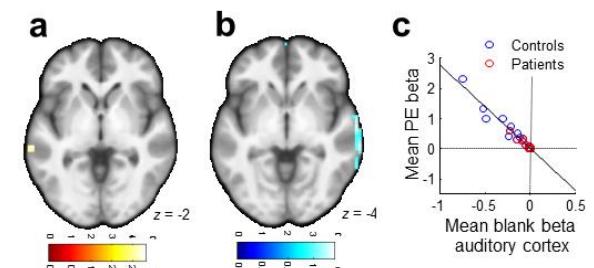


Fig. 6. (a) AVH-related activation in the auditory cortex of patients. (b) Decreased prediction errors in patients. (c) Correlation between prediction errors and resting activity in auditory cortex.

Recruitment Patients will be recruited through referrals from mental health clinicians in collaboration with the Division of Translational Imaging, directed by Dr. Abi-Dargham (co-mentor). Referrals will be obtained from the Lieber Schizophrenia Research Clinic (which follows over 70 research patients with schizophrenia annually), the Washington Heights Community Service, and private practices. The Division of Translational Imaging recruits more than 15 drug-free patients per year to research protocols using these sources. Considering that we have pre-screened over 20 patients, we do not anticipate difficulties in recruiting 40 patients over 3½ years. *Healthy controls* will be recruited through community outreach and public advertisements. Dr. Peterson's laboratory participant database will be used to recruit a control sample with a demographic profile that matches the clinical sample. Considering that we have pre-screened over 30 healthy participants we do not anticipate any difficulties in reaching the recruitment goal of 20.

Screening (see Protection of Human Subjects)

Clinical Assessment The following battery of structured interviews and scales will be used to confirm the diagnosis of schizophrenia or schizoaffective disorder, assess comorbidity, and measure symptom severity.

General assessment. The **SCID-I**⁴⁹ will be the main diagnostic instrument used to confirm the referral diagnosis and assess comorbid disorders. We will also ascertain the age of onset of psychotic symptoms, duration of untreated psychosis, **lifetime severity of psychotic symptoms through the LDPS**⁵⁰, and family history of Axis-I disorders through the Family History Screen (**FHS**)⁵¹.

Severity of psychotic symptoms. The Positive and Negative Syndrome Scale (**PANSS**)⁵² will be used to assess the severity of positive, negative, and general symptoms. In addition, the Psychotic Symptom Rating Scales (**PSYRATS-AH**)⁵³ and the Auditory Hallucinations Rating Scale (**AHRS**)⁵⁴ will be used to measure the severity of several domains of hallucinations. The Beck Cognitive Insight Scale (**BCIS**)⁵⁵ and the Beliefs About Voices Questionnaire (**BAVQ**)⁵⁶ will be used to assess the degree of insight into AVH.

Severity of mood symptoms. The Hamilton scales for anxiety (**HAM-A**)⁵⁷ and depression (**HAM-D**)⁵⁸ will be used to quantify the severity of anxious and affective symptoms on the scanning day. The Calgary Depression Scale for Schizophrenia (**CDSS**)⁵⁹ will be administered as well to better differentiate depressive from extrapyramidal and negative symptoms.

Qualitative AVH questions. All 20 phenomenological features of AVH identified by Stephane et al.⁴⁶ will be evaluated at the initial assessment and specific examples of hallucinatory content will be collected. Immediately after the scan, patients will be debriefed in a room at the scanner suite to confirm that they experienced AVHs in the scanner, quantify their approximate frequency, and evaluate their phenomenology.

Neuropsychological and Social Assessment (assessed on the same day as the scanning session)

Intellectual and cognitive functioning. All participants will undergo testing with the Wechsler Abbreviated Scale of Intelligence (**WASI**)⁶⁰, which provides a quick screening of verbal and non-verbal domains of intellect. In addition, participants will be administered the Brief Assessment of Cognition in Schizophrenia (**BACS**)⁶¹. *Socioeconomic status* of participants and their families will be evaluated with the **Hollingshead Index of Social Status**⁶². *Handedness* will be evaluated with the **Edinburgh Handedness Inventory**.⁶³

Imaging Procedures

Participant Preparation Before scanning, participants will be explained the cost of the procedure and the importance of remaining awake and still in the scanner for the acquired data to be usable. We will combine relaxation training, frequent praise and reminders to remain awake and still, and an inflation pillow with over-the-ear headphones taped to the participant's forehead. Using these strategies, Dr. Peterson's laboratory has obtained over 2000 high-quality, motion-less scans in pediatric and adult populations that are difficult to scan. All participants will undergo a practice session of the task (see Task) ~1 hour before scanning.

3T MRI Pulse Sequences Images will be acquired on a GE Signa 3T scanner, equipped with the highest performance (CRM) Shielded Gradient Coil enabling ultra-fast echo-planar images (EPI) and an 32-channel, phased-array head coil. T1-weighted sagittal localizing images will be acquired followed by a 3D spoiled gradient recall (**SPGR**) image and a **high-resolution EPI** volume for coregistration with the functional EPI series. Axial **EPI series** with an effective resolution of 3.5 mm³ and whole-brain coverage (TR = 2000 ms, TE = 28 ms, 77° flip angle, slice thickness 3.5 mm, 22.4x22.4 cm field of view, 64x64 matrix) will be acquired both with **sparse sampling (1st phase**, 4 series, 3 volumes per cluster, intercluster interval = 10 s; **Fig. 7**) and **continuous sampling (2nd phase**, 1 series). This sparse-sampling or "silent" fMRI sequence minimizes brain activation induced by scanner noise⁶⁴ by capitalizing on the normal delay in the BOLD response with respect to the stimulus that evokes it (**Fig. 7**): on each trial, it acquires images around the time when stimulus-evoked responses peak and then stops acquiring images for the period of time during which scanner-noise-evoked responses peak, thereby recording responses to stimuli of interest but not responses to scanner noise. Anatomical scans will be reviewed by a neuroradiologist. Total scan time per participant will be ~90 minutes.

Task: Speech Discrimination Task

In the **1st phase**, participants will complete a low-cognitive-demand auditory task in which they will simply have to respond to inquiries about the absence or presence of speech percepts on each trial. Auditory stimuli (speech, non-speech, or no stimulus) will be presented in the absence of scanner noise, prior to scanning periods within a sparse-sampling sequence. The question "did you hear any voices?" will prompt a response at the end of each trial. **Participants will be instructed to respond to the question**

via button press if they heard voices during that trial, regardless of the type or presumed origin of the voices, and withhold the response otherwise. AVH trials will be formally operationalized as trials in which no stimulus is presented but during which patients indicate perceiving speech (i.e., speech percept without a corresponding stimulus; see Preliminary Data D1.3 using this definition). The remaining trials will be categorized as speech, non-speech, or blank trials (no speech percept and no stimulus). Non-speech stimuli signaled as speech-positive and speech stimuli signaled as speech-negative are anticipated to be very rare (based on our preliminary data) and will be discarded. **Stimuli.** Trials containing speech stimuli (28%), non-speech stimuli (28%), or no stimuli (44%) will be arranged pseudo-randomly. Seventy unique speech stimuli consisting of sentences (from short phrases to complete sentences; e.g., "you're bad", "make yourself at home and call me if you need anything"; mean duration \pm s.d., 2.28 ± 1.18 s), obtained from 20 speakers, were developed specifically for this project to manipulate speech features relevant to AVHs⁴⁶ independently across trials (including content: derogatory/neutral, related/unrelated to patient; linguistic features: 2nd/3rd person, low/high linguistic complexity; and acoustic features: gender of speaker, one/several speakers, high/low [60/50 dB] volume, and low/high clarity). Non-speech stimuli (including non-speech vocal sounds such as breathing and coughing, and non-vocal sounds such as animal cries and mechanical sounds) were obtained from a public database (freesounds.org). Speech and non-speech stimuli, digitized at a 16 bit/44.1 kHz, are matched on mean duration, amplitude and energy. Stimuli will be delivered binaurally via piezoelectric headphones. **Task structure.** Each trial will last 16 s. Visually, each trial will include a 13-s fixation crosshair followed by a 3-s question, "did you hear any voices?". No scanning will take place during this 3-second question (while button responses are recorded) or in the first 7 s of each trial. Intermittent scanning periods will start at 7 s into the trial and last for 6 s. Jittered sound stimuli will be presented 4 ± 0.175 s (s.d.) prior to periods of image acquisition. Four 13-minute blocks each will contain 50 trials, for a total of 200 trials presented over 55 minutes. Blocks with high probability of speech (0.44) versus non-speech (0.11) will alternate with blocks with low probability of speech (0.11) versus non-speech (0.44) in a counterbalanced order. The probability of blank trials will be constant across blocks (0.44).

In the **2nd phase**, participants will not hear stimuli or perform any active task (resting state). They will lie still with their eyes open while continuous volumes are acquired for 13 minutes.

Ratings and debriefing. At the end of each block, participants will rate a series of questions, each on a 10-point visual analogue scale, regarding their emotional state and the features of speech percepts heard throughout the block. These ratings will also be acquired after the resting-state block to assess information about any AVH experienced during this block. A psychiatrist will debrief patients immediately after scanning to corroborate the experience of AVH and estimate the number and features of AVH during the scanning session and during the resting-state block in particular. **Considerations.** (1) We intentionally will not ask patients to signal the onset of AVHs with a button press so as to avoid potential confounds related to planning and execution of the motor response; we will inquire about speech percepts after each brief scanning period. (2)

The lack of control over the occurrence of AVHs poses some challenges. AVH may co-occur with speech trials, complicating the calculation of positive PEs (i.e., PEs on speech trials). Group analyses will control for number of AVH in the scanner, taking into account that differential correlations between positive (vs. negative) PEs and number of AVH could reflect an artifact. We ruled out the possibility of having patients signal AVH and speech in separate ways because it would inevitably entail increased cognitive demand (i.e., it would require divided attention and source discrimination, likely abnormal in patients) and differing tasks/strategies across groups, even if a control condition was introduced in the healthy group. (3) AVH-related activations will likely be jittered relative to image acquisition and may thus be weaker than stimulus-evoked activations, a

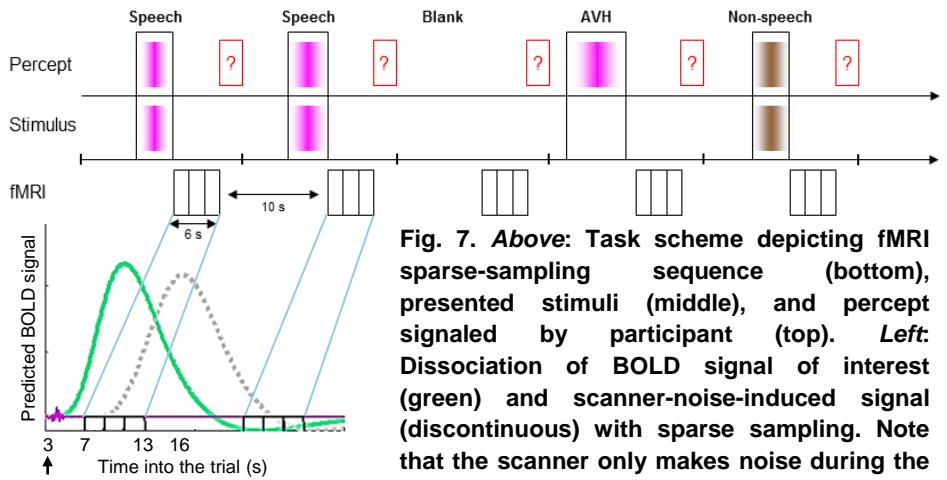


Fig. 7. Above: Task scheme depicting fMRI sparse-sampling sequence (bottom), presented stimuli (middle), and percept signaled by participant (top). **Left:** Dissociation of BOLD signal of interest (green) and scanner-noise-induced signal (discontinuous) with sparse sampling. Note that the scanner only makes noise during the 6-s clusters of image acquisition.

problem that is inherent to the study of spontaneous, subjective phenomena such as AVH. To improve comparability with AVH, speech presentation will also be jittered (see *Task structure*). Moreover, the preliminary results with this paradigm show its ability to capture AVH-related activations without the confounds that conventional fMRI studies have with regard to scanner-noise-induced activations and saturation effects, which are even more likely to underestimate and mis-model AVH-related activations.

fMRI Image Processing and Analyses will be conducted with SPM8 and custom Matlab scripts.

Preprocessing will include coregistration of anatomical SPGR and high-resolution functional EPI volumes, resampling to 3x3x3 mm and spatial smoothing (FWHM=6x6x6 mm). Images will be then corrected for motion and for T1-decay artifacts by including volume-specific intercepts for the 3 volumes within each acquisition cluster.⁶⁴ Each 3 residualized volumes will be then averaged within each cluster producing an image per trial.

Regression Models Preprocessed images (one corresponding to each trial) will be entered into a general linear model (GLM) in SPM8. An advantage of the sparse-sampling approach is that no convolution with a hemodynamic response function (HRF) is required and thus this analysis does not have strong assumptions about the HRF shape. The first-level **GLM₁** model will include 4 regressors corresponding to each trial type (speech, non-speech, blank and AVH) along with session-specific intercepts. Planned contrasts include [AVH versus blank] and [all stimuli versus blank]. **GLM₂** will include session-specific intercepts and 2 regressors corresponding to model-derived estimates (see *Model-based Analysis*) of speech prediction error and speech prediction. Extended models will also explore the influence of stimulus features (volume, gender, pitch, linguistic complexity, and content emotionality). Second-level, mixed-effects models will test within- and between-group effects of the prediction-error beta from **GLM₂** (Aim 1) and group-effects of the contrast [AVH versus blank] from **GLM₁** (**main contrast for Aim 2**). **Functionally-defined regions-of-interest** (fROIs) within auditory cortex will be defined bilaterally for each subject based on the contrast [all stimuli versus blank].

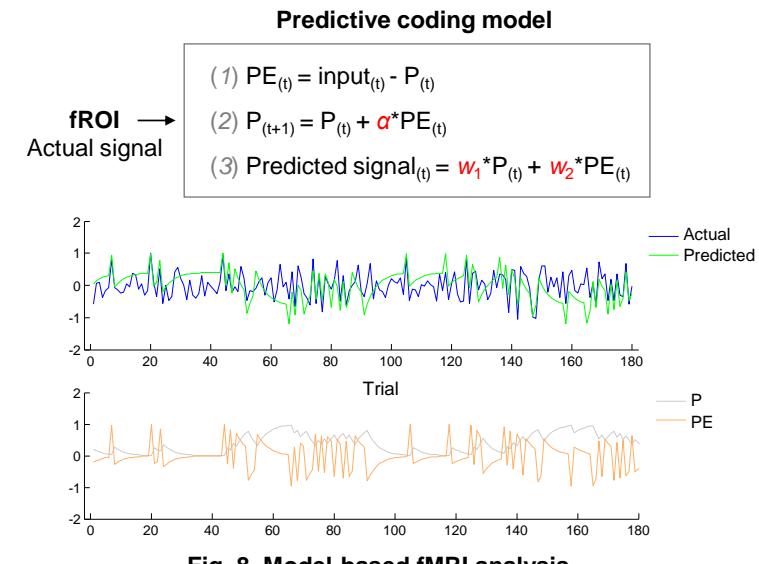
Model-based Analysis (Fig. 8) Signal from the fROIs in the auditory cortex will be used to fit a predictive-coding algorithm based on a delta rule implementation akin to reinforcement-learning models.³¹ This algorithm models prediction errors (PE) as the difference between the actual speech input (input=0 for no speech, input=1 for speech) and the predicted speech input (from lowest expectation P=0 to highest expectation of speech P=1) and updates predictions based on a learning rate α . It assumes that the ROI signal is a weighted sum of P and PE, with weights w_1 and w_2 . The minimization function `fmincon` in Matlab will be used to find the best-fitting solution for the unknown parameters (w_1 , w_2 , α) by minimizing the difference between the predicted (green) and the actual fMRI signal (blue), and obtain trial-by-trial estimates of P and PE (Fig. 8 bottom panel). To ensure non-circularity and reduce noise in this procedure, the best-fitting α for the group will be used to estimate the individual time-series of P and PE used in **GLM₂** to find whole-brain correlates of these signals.

Data Management *Clinical Data:* A relational, password protected database in Access will be stored on a secure server. Hard copies of data will be stored in locked locations with restricted access. Database copies on CDs are stored separately for safety. *Imaging Data:* Data will be controlled for quality at the scanning console, then transferred to my computer over a dedicated fiberoptic network through a secure Storage Area Network (SAN) supporting backup, archiving, data migration, and data sharing among different servers.

Hypothesis Testing (and Power Analysis)

Aim 1: To determine the neural correlates of auditory-verbal predictions in patients with schizophrenia with and without hallucinations and healthy controls. Controls are hypothesized to display auditory-verbal predictive signals (specifically, prediction-error signals) in the auditory cortex (**Hypothesis 1.1**) and these prediction-error signals will be reduced in **high-AVH patients compared to low-AVH patients (Hypothesis 1.2)**.

Methods: To assess statistical significance in the second-level GLMs, I will examine the parameter estimates, confidence intervals, and p-values of the component terms in an analysis of mixed effects. I will use Gaussian Random Field theory and false discovery rate to correct p-values and protect against Type-I error. Thus, p-values <.05 corrected at the cluster level will be considered significant. **Power Analysis:** I assume the use of



a GLM for fMRI measures of task-related activation. Let Y_j be the average task-related signal change in each voxel within the *a priori* ROIs for the j -th subject. The linear model is given by $Y_j = \beta X_j + \varepsilon_j$, where $\varepsilon_j \sim N(0, \sigma^2)$. For within-group tests (**Hypothesis 1.1**), X_j is simply an intercept term β_0 representing the average prediction-error effect for the group. For between-group tests (**Hypothesis 1.2**), X_j includes an intercept term and two groups (e.g., High-AVH patients vs. controls), $\beta = (\beta_1, \beta_2)$, and β_1 represents signal differences between two groups. The null hypotheses are $H_0: \beta_0 = 0$ and $H_0: \beta_1 = 0$, respectively, and t-tests can be applied. With 20 individuals in each group, the effect sizes (>.8 power, 1-sided test, alpha=0.05) are 0.58 for the within-group hypothesis (**Hypothesis 1.1**) and 0.8 for the between-group hypotheses (**Hypothesis 1.2**). Based on the effect sizes for the preliminary data, however, the `fmripower` tool estimates that the power for the between-group tests within the ROIs would be over 90%, so the above effect-size estimates might be conservative.

Possible Confounds: Task accuracy, medication history, motion, gender, age, height, weight, minority status, handedness, IQ, socioeconomic status, and severity of depression or anxiety (HAM-D or HAM-A) will be included as nuisance covariates in the above models if they differ between groups. Because, in contrast to our hypothesis, AVH could potentially disrupt speech predictions and induce an artifact on the task, the number of AVH in the scanner will also be controlled for. **Exploratory Analyses:** Dimensional effects of lifetime severity of AVHs across all patients will also be assessed in a regression analysis. An alternative computational model that considers AVH as speech input will be also tested. To overcome the limited power of our study, ROI-based analyses will be conducted if necessary. Effects of subjective emotions on PE effects will be analyzed. Our manipulation of speech features will permit additional analyses, e.g., into the bases of pitch processing. Lastly, the resting-state data will also be analyzed to assess network-level connectivity.

Aim 2: To map neural activations associated with auditory-verbal hallucinations (AVH) in patients with schizophrenia. High-AVH patients are hypothesized to have increased activation in the auditory cortex and limbic regions and decreased activation in the thalamus as assessed through the critical contrast of AVH trials versus blank trials (**Hypothesis 2**), trials in which no stimulus is presented and which only differ on the subjective speech percept (present in AVH trials and absent in blank trials). **Methods** are analogous to those in Aim 1.

Power Analysis: I assume the use of a GLM for fMRI measures of AVH-related activation. I will use a within-group test based on the linear model $Y_j = \beta X_j + \varepsilon_j$, where X_j corresponds to an intercept term and β_0 represents the average signal differences between AVH and blank trials within High-AVH patients. The null hypothesis is $H_0: \beta_0 = 0$ and the effect size (>.80 power, 2-sided test, alpha=0.05) is 0.66 for a one-sample t-test in 20 patients with AVH. Unlike in the analyses related to Aims 1 and 3, high-AVH patients who do not experience AVH in the scanner will not be included in this analysis (the effect size is 0.7 with a sample size of 18, assuming that, based on our preliminary data, ~10% of high-AVH patients may not hallucinate in the scanner).

Exploratory Analyses will take into account the difference of AVH episodes across participants and give proportional weight to participants based on the number of AVH episodes (weighted t-test). AVH trials will also be compared to speech trials matched by speech features. To confirm that AVH-related activations occur in the auditory cortex, the accuracy of a support vector machine (SVM) classifier in discriminating between AVH and blank trials will be tested (Machine Learning course, Training Goal 1). The relationship between AVH activations and clinical measures of AVH will be assessed in regression analyses.

Aim 3: To determine the relationship between auditory-verbal predictions and auditory-verbal hallucinations (AVH) in schizophrenia. The magnitude of the prediction-error deficit is hypothesized to correlate with the magnitude of resting activation in the auditory cortex across all 60 participants (**Hypothesis 3.1**). Additionally, the speech predictions (P) induced by the task are hypothesized to reduce the occurrence of hallucinations (frequency of AVH) in patients with AVH (**Hypothesis 3.2**). **Methods** are analogous to those in Aim 1. For hypothesis 3.2, the proportion of trials in which no stimulus is presented but in which the patient reports AVH will be estimated separately for trials with above-median and below-median P. Thus, for each participant we will obtain two values corresponding to the percentage of AVH for high-P and low-P trials.

Power Analysis: Hypothesis 3.1 can be tested through a one-sided Pearson's (or nonparametric) correlation across all 60 participants. The estimated effect size (>.80 power, 1-sided test, alpha=0.05) is 0.3. For hypothesis 3.2, I will use a within-group test based on the linear model $Y_j = \beta X_j + \varepsilon_j$, where X_j corresponds to an intercept term. The null hypothesis is $H_0: \beta_0 = 0$, where β_0 corresponds to the average difference in the percentage of AVH between high-P and low-P trials for the group. The estimated effect size for this t-test (>.80 power, 2-sided test, alpha=0.05) is 0.66. **Exploratory Analyses:** Hypothesis 3.1 will also be tested separately within each subgroup and particularly within the high-AVH patients, especially if this subgroup shows differentially increased variance in resting activation of the auditory cortex. Hypothesis 3.2 will also be tested in a mixed logistic regression predicting AVH (0=absence of AVH, 1=presence of AVH) based on the subject and the level of P (0=low to 1=high). If this does not yield positive results due to the limited power in preliminary analyses, a longer version of the task will be used outside of the scanner to test this hypothesis.

Treatment intervention (for future R submission) I will design a computer-based intervention for sensory prediction training (SPT) that builds on (1) our preliminary findings and prior work indicating that (2) healthy individuals have robust behavioral benefits for perceptual discrimination based on predictive contexts⁹, and that (3) context-focused cognitive training normalizes behavioral and neural deficits in the use of contextual information in schizophrenia and senescence^{65,66}. SPT will aim at improving the use of contextual information such as the block-wise probability of stimuli by providing feedback that is selectively contingent on the benefits for perceptual discrimination in predictive versus non-predictive contexts (e.g., one goal would be to enhance discrimination of speech versus non-speech stimuli specifically in contexts that predict a higher probability of speech). In years 4½-5, I will obtain pilot data in health (to assess behavioral effects) and schizophrenia (to assess preliminary efficacy in an open case series) to support the feasibility of this SPT and, if needed, I will seek funding after year 5 to collect additional data (e.g., R21). My ultimate aim is to conduct a randomized clinical trial in AVH patients to test the efficacy of an SPT program in improving AVH. The purpose would be two-fold: positive results would position sensory predictions as a valuable therapeutic target (and potentially a useful marker of treatment response) and would additionally prove a *causal* link between sensory predictions and AVH. Finally, yoking the current fMRI paradigm to the clinical trial would help evaluate whether SPT improves hallucinations by ameliorating functional deficits in predictive signals.

Expected Outcomes and Future Directions This proposal is expected to identify abnormalities in predictive coding in patients with hallucinations. Findings of reduced prediction-error signaling in sensory regions will support the proposed model of positive symptoms in schizophrenia, which hypothesizes that deficits in sensory prediction errors underlie hallucinations. A direct link between prediction-error deficits and AVH will provide, for the first time, fundamental insights into the mechanisms underlying the generation of positive symptoms. This study will provide a model for the empirical investigation of mechanisms of mental illness and for the application of computational neuroscience in psychiatry. Based on findings from this study, we will develop a comprehensive computational model of AVH **that could potentially guide the development of pharmacological and non-pharmacological treatments that target sensory predictions**. Our study constitutes a first step towards the identification of primary mechanisms of psychotic symptoms in schizophrenia allowing the development of novel treatments to directly target these mechanisms (in line with my planned R01 submission). My long-term goals thus align with the NIMH strategic plans to promote brain research into the causes of mental disorders and to develop improved and tailored treatments for these disorders.

PROTECTION OF HUMAN SUBJECTS

The human subject research proposed in this application meets the NIH definition of "clinical" research. The collection of MRI, clinical, and neuropsychological data in the proposed study has been approved until 08/24/2013 by the New York State Psychiatric Institute and Columbia University Institutional Review Board under protocol #6435R: fMRI studies of the brain in health and illness. Approval of this protocol will be extended upon receipt of this award. All staff members on the research team are required to receive training in the protection of human subjects. This includes both Good Clinical Practices at Columbia University (entitled Health Sciences: Protection of Human Research Participants (GCP) for Patient-Oriented Clinical Investigators) and the Collaborative Institutional Training Initiative (CITI).

Proposed Involvement of Human Subjects In this study, 40 drug-free subjects with schizophrenia (20 with frequent AVH and 20 without AVH; see also Recruitment and Consent Procedures) and 20 healthy controls will be recruited. We will group-match the healthy control subjects for relevant variables, such as age, ethno-racial categories, socio-economic status, IQ, and handedness. The two patient groups (AVH and non-AVH) will be additionally matched for clinical variables other than AVH (severity of PANSS subscores other than PANSS-P3 *hallucinatory behavior*). All subjects will undergo diagnostic evaluations, followed by MRI scanning and neuropsychological testing. These procedures (described in the Research Strategy) will typically occur on one day and take approximately 5 hours to complete.

Inclusion Criteria All participants will be 18-55 years old, medically-stable, and fluent English-speakers. Patients will meet DSM-IV-TR criteria for schizophrenia or schizoaffective disorder. Patients will be referred from clinicians who follow them regularly. AVH patients will additionally meet the DSM-IV-TR criterion A2 *hallucinations*; they will report clearly hearing voices in the absence of corresponding external speech at least daily, several times per day, in the past two weeks. Around 40% of patients with schizophrenia do not experience AVH in their lifetime. Patients without AVH will be recruited who have never reported hallucinations in the auditory modality.

Exclusion criteria for all participants will be 1) pregnancy; 2) current or lifetime history of a major medical or neurological problem (e.g., unstable hypertension, epilepsy, head trauma); 3) presence of ferromagnetic devices or implants in the body; 4) recent history of substance use disorders within the last 3 months; 5) active suicidal ideation; 6) IQ <80; 7) current major affective episodes (mania or major depressive episode); 8) hearing impairment or any hearing disorders. In addition, healthy control subjects will not have any DSM Axis-I psychiatric disorders. Because depressive symptoms frequently accompany schizophrenia, we will include patients with mild or moderate depressive symptoms (HAM-D score < 24) who do not meet full criteria for current Major Depressive Episode. We will assess the effects of depression on our imaging effects (see hypothesis testing in Research Strategy-Approach).

Sources of Research Material Research material will be obtained from subjects who participate in this study for research purposes only. Research material will include demographic information such as age, race, medical and psychiatric history, parental education and occupation. It will also include MRI scans, psychiatric diagnostic interviews, ratings of symptom severity, and neuropsychological testing (detailed in Research Strategy). Medicaid and social security numbers will be recorded. Data linked to participant identities will be coded by number and kept in locked, confidential files and/or on password-protected computers behind firewalls at NYSPI with Dr. Horga (PI).

Screening A preliminary phone screening will be conducted for all potential participants. They will be informed about the scanning and other study procedures and will be screened for any metals on or in their bodies that would preclude their participation. Eligible patients will also be screened in person and their capacity to consent will be assessed based on the MacArthur Competence Assessment Tool-Clinical Research (**MacCAT-CR**) by an independent clinician. If participants meet inclusion criteria and, in the case of patients, they are capable of consenting, we will obtain written informed consent for their participation. Then, participants will be scheduled for a 3-hour diagnostic and neuropsychological assessment and a 2-hour MRI session; they will be offered to complete these procedures in one or two days. A trained research assistant (RA) hired for this project will perform the diagnostic and neuropsychological assessment. The staff at Dr. Peterson's lab will assist in training and supervising the RA on all diagnostic and neuropsychological measures. I will supervise the assessments as I become proficient with all diagnostic measures (see Training Goal 4). Assessments will take place in neuropsychological testing suites at the NYSPI.

Recruitment and Consent Procedures Please see the Research Strategy for further details on recruitment.

Patients will be recruited through referrals from mental health clinicians to ensure fidelity and stability of diagnoses. Referrals will be obtained from the Columbia University psychiatry clinics, the Lieber Schizophrenia Research Clinic (a specialized clinic for schizophrenia with approximately 70 outpatients participating in research studies, with a recruitment rate of ~6 patients/month) and the Washington Heights Community Service (which includes a 22-bed inpatient unit and 2 outpatient clinics providing services to Northern Manhattan). On a biannual basis (or more frequently if needed), Dr. Horga (P.I.) will attend clinical meetings at the outpatient clinics to request referrals directly from clinicians in the clinic. In addition, he will attend clinical meetings at the Lieber Clinic weekly. Over 20 eligible patients have already been pre-screened for this study. All clinicians will be provided with flyers with basic research and contact information.

Patients will be recruited in collaboration with the Division of Translational Imaging, following their IRB-approved PET protocol with **drug-free patients** ("Imaging Cortical and Extrastriatal Dopamine in Patients with Schizophrenia and Healthy Controls"; Principal Investigator: Anissa Abi-Dargham, MD). Patients will be maintained free of psychotropic medications for a period of 3 weeks before participating in the imaging procedures. No patients will be tapered off of medications solely for research purposes. One group of patients who will be recruited into/referred for this study are outpatients followed by clinicians in the Washington Heights Community Service clinics or the Lieber Clinic who are already medication free. We will not recruit patients who are admitted to an inpatient unit for clinical reasons. Patients will be treated after the procedures with medications until they are stable prior to discharge. The second group of patients who will be recruited/referred for this study are outpatients who are on medications but require a change due to either ineffectiveness or intolerable side effects. These determinations will be made jointly by the patient and his/her treating psychiatrist. This group of patients will be admitted to the 5-South inpatient unit at NYSPI for their medication taper and tapered off of their medications by the attending psychiatrists on the unit, in consultation with the patients' outpatient psychiatrists. The patients will remain in the hospital for the entire three weeks during which they are medication free and until they receive their scans, and then will receive treatment. If, at any time, either the patient, inpatient psychiatrist, outpatient private psychiatrist, or study physician feels that the patient's clinical status is significantly worsening during the taper or medication free period, the patient will be treated appropriately and terminated from the protocol. Any patient who requests to be re-started on antipsychotic medication will be exited from the antipsychotic-free study period. Criteria for Clinical deterioration include: (1) observed or reported aggressive/self-injurious behavior; (2) agitation; or (3) subjective distress/discomfort, or (4) CGI of 6 or 7. During the

taper and neuroleptic-free period patients may take lorazepam PO, up to a maximum of 8 mg per day. The Division of Translational Imaging advertises this protocol broadly, including descriptions in mailings to researchers, clinicians, and family groups, and may be published in NAMI and related organization newsletters, professional society and OMH publications, local newspaper, and the Internet with the aim of reaching eligible patients. The Division of Translational Imaging recruits more than 15 drug-free patients with schizophrenia per year and has a combined 45 years of experience with medication tapers in patients with schizophrenia in the context of research studies.

Healthy controls will be recruited through community outreach and public advertisements (fliers, letters, web postings, and newspaper advertisements). Healthy control subjects will also be contacted through mailings and subsequent telephone calls to addresses that have been purchased from a national telemarketing company. The recruitment resources in the Division of Translational Imaging and the database of healthy controls in Dr. Peterson's laboratory will also be used to recruit subjects with a demographic profile (ZIP code, age, gender, ethnicity, income level) that matches that of the clinical sample. Using this database in the past has produced a recruitment ratio of ~90% of eligible participants, so we do not anticipate any difficulties in reaching the recruitment goal of 20 healthy participants. Indeed, over 30 eligible healthy controls have already been pre-screened and are interested in participating in this study.

Assessment of Capacity to Consent Special consideration will be given in the consenting process to patients with schizophrenia. More specifically, procedures will be implemented to assess their capacity to consent. Under the following circumstances, adult subjects cannot give consent to participate in this study: the subject does not demonstrate a free choice to consent, or he/she does not demonstrate an understanding of the procedures, alternatives, and potential risks and benefits of the study, and that participation is voluntary. The independent assessment of capacity to consent will be conducted, signed, and dated by the designated clinical monitor for all adult subjects with schizophrenia. The clinical monitor is a psychiatrist or a licensed clinical psychologist that is neither the principal investigator nor affiliated with this research study. Persons that will be designated to assess capacity to consent are psychiatrists or licensed psychologists from the Department of Psychiatry at Columbia University or the Washington Heights Community Service, who are not members of our research team. An independent psychiatrist will assess the subject's capacity to provide informed consent using the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) interview that has been adapted to objectively document the subjects understanding of the key elements of this study. The MacCAT-CR score can range from 0-26. We will not use an arbitrary cut-off score below which a subject would not be eligible for participation, but rather, leave it to the independent clinician to make an overall judgment of the subject's understanding of the study and their ability to provide informed consent. If a patient has difficulty understanding all study elements during the consent process, the procedures will be explained again by a member of the research team. If there is still doubt about the subject's understanding of the key elements of the study and ability to provide informed consent, the subject will not be enrolled in the study.

Informed Consent In the consent forms and in the consent discussion, potential participants will be advised fully of the study procedures, the amount of time required of them, the possible risks and benefits, the voluntary nature of their participation, their right to refuse participation without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the PI. Potential participants will be encouraged to ask questions about any aspect of the study that is unclear to them, and those questions will be addressed carefully to clarify any uncertainties. Patients will be informed that this is not a treatment study. Those interested in treatment will be told of treatment options within the Lieber Schizophrenia Research Clinic and given the option to seek treatment immediately.

Pregnancy Testing All female subjects will be required to have a pregnancy urine test prior to the MRI scan. The test will be conducted after the signing of the consent/assent forms, will be conducted on site, and will be paid for by the study. Urine samples will be collected and pregnancy tests done on the day of the MRI scan. The clinical research team will discuss the results of the pregnancy test with the subject. If the pregnancy test is positive, the subject will be excluded from further participation in the study and encouraged to consult with their primary physician or family planning clinic. Appropriate referrals will be made upon request.

Confidentiality In the consent forms, subjects will be told that the information they provide and all findings will be kept strictly confidential. Data collected with identifying information will be coded by number and stored in locked cabinets or in password-protected computer files. Subject identity will not be revealed in the presentation or publication of any results. Data from subjects will only be available to Federal, State, or other regulatory agencies, as well as institutional personnel (who may review records as part of routine audits). In situations where it is determined that a subject is at significant risk for self-or-other destructive behavior, including current and/or previously unreported child abuse and neglect, the PI and the staff are required by law to report to the authority. All staff working on the project will be educated about the importance of strictly respecting patient confidentiality. An authorization form to access personal health information (PHI) under the Health Insurance Portability and Accountability Act (HIPAA) will be presented to subjects.

Potential Risks The risks associated with participation are: 1) distress from discussion about psychiatric symptoms; 2) fatigue from neuropsychological testing, 3) risks of being off medication and 4) risks associated with MRI scanning.

1) Distress from thoughts or discussion about psychiatric symptoms: Some subjects may experience distress or anxiety related to participating in these procedures. Subjects will be monitored throughout the procedures, and they will be encouraged to report any concerns. A psychiatrist will be available to assist the subject if needed, and subjects will be removed from the protocol if their distress or anxiety becomes intolerable. Also, each study participant will be provided with a 24-hour emergency contact number.

2) Fatigue from neuropsychological testing: Some subjects experience fatigue during neuropsychological testing. Subjects will be encouraged to report fatigue and short breaks will be offered throughout testing.

3) Risks of being off medication: For the group of patients who will have their medications tapered during this study (i.e., those patients who are not already off of medications), symptoms of illness may worsen. For example, when taken off medication, some patients with schizophrenia experience more frequent or bothersome hallucinations, delusions (fearful or troubling false beliefs), anxiety, confusion, anger, changes in mood, and problems with sleep. We anticipate that more than half of the patients who will have their medications tapered will have at least some worsening of their symptoms. There is also the chance that symptoms will take longer to resolve after the medication-free period than if medication had been provided continuously. It is worthy of note that many patients with schizophrenia have treatment histories which include brief or extended periods of medication noncompliance. We will exclude patients who, based on review of past experiences while medication-free, e.g. while non-compliant with medication, experience serious aggressive or self-destructive behavior. Other patients judged to be a serious risk for such behavior are also excluded. Patients who are unable to tolerate the antipsychotic medication free period and who do not respond to benzodiazepines and/or non-pharmacologic treatments will be excluded. It is also important to note that many currently available and prescribed antipsychotic medications produce serious side effects.

4) Risks Associated with MRI Scanning: The risks of MRI scanning can be classified into one of four categories, those associated with a) Acoustic Noise Levels, b) Gradient or Time-Varying

Magnetic Fields, c) Radiofrequency (RF) Magnetic Fields, and d) Static Magnetic Fields.

a. Acoustic Noise Levels: The acoustic noise associated with MR imaging is related to the mechanical movement of the gradient coils during the scanning process.

FDA Guidelines: "The acoustic noise levels associated with the device must be shown to be below the level of concern established by pertinent Federal Regulatory or other recognized standards setting organizations. If the acoustic noise is not below the level of concern, the sponsor must recommend steps to reduce or alleviate the noise perceived by the patient." Current FDA guidelines follow the regulations of the International Electrotechnical Commission (IEC) Standard 601-2-33, which stipulate that for MR equipment used in medicine, hearing protection is required when the system can produce acoustic sound levels above 99 dBA (maximum A weighted r.m.s.) and that the protection should be able to reduce noise levels to below 99 dBA.

The FDA has approved systems for which noise levels have been quantified, ranging up to 105 dB RMS for scanners operating at field strengths of 1.5 Tesla. It is important to note that the static magnetic field strength is only one factor, and not necessarily the most important one, in determining acoustic noise. Among the factors listed above, the design and construction of the gradient coils plays a major role in the noise level that MRI scanning produces. Therefore, noise levels are not necessarily greater when scanning at 3.0 T compared with 1.5 T field strengths. It is nevertheless possible that, in some circumstances, our system could produce noise levels higher than 99 dB, as do many clinical systems operating at lower field strengths.

Summary: The acoustic noise levels perceived by human subjects when undergoing MRI examination in our 3.0 Tesla magnet constitutes a non-significant risk; specifically, our system will not be operated in a way that will present more noise to human subjects than is recommended by the FDA.

b. Time-Varying Magnetic Fields: The concern about the time-varying magnetic fields used in MRI is that these can, in some instances, induce stimulation of peripheral nerves, thereby producing sensations such as 'twitching' or 'tingling'. In very rare instances, this nerve stimulation can be painful. Nerve stimulation is particularly likely when subjects are physically positioned in a way that increases the likelihood of inducing stimulation, such as with hands clasped or arms folded. It should be noted that the parameter of interest here, dB/dt (the rate of change in the magnetic field per unit time), is not a function of the strength of the static magnetic field, so evaluating risk in a 3T MRI scanner involves the same considerations as evaluating other MRI systems operating at lower magnetic field strengths (i.e., the same issues apply to all the commercially available, FDA approved scanning systems). Thus, it is the *gradient system only* that needs to be evaluated to determine the risk of producing nerve stimulation.

FDA Guidelines: The FDA Guidance of 1995 was developed specifically to consider the fact that many clinical systems were capable of exceeding levels of dB/dt that could produce nerve stimulation. It was originally considered that a warning level should be implemented to guard against peripheral nerve stimulation, but the FDA finally concluded that: '*... this warning level is not considered critical since there are no harmful effects associated with mild peripheral nerve stimulation*'. The current guidelines therefore include monitoring procedures to help avoid painful peripheral nerve stimulation, and without specific dB/dt limitations.

Summary: The gradients used in our 3.0 Tesla MRI system will typically be operated at levels below those considered to be negligible according to FDA guidelines. Our system, like most commercially available, FDA-approved systems, does have the capacity to exceed this level, but it will include the same safeguards that are included in other FDA-approved clinical systems. Furthermore, policies and procedures will be implemented according to FDA guidelines to avoid the possibility of painful peripheral nerve stimulation. Therefore, in all circumstances the system will be operated in a way that poses nonsignificant risk to the participant.

c. Specific Absorption Rate (SAR): MRI scanning induces some heating of body tissues. This specific absorption rate (SAR) that determines heating is the amount of radiofrequency (RF) energy

deposited (typically by a coil or “helmet”-like apparatus placed over the subject’s head) per unit volume of tissue per unit time. The SAR for RF radiation is primarily related to the amplitude of RF power, the duration of the RF pulse, the type of RF coil used, the frequency of RF radiation, the resistivity of the tissue, the configuration of the anatomical region being examined, and several other parameters.

FDA Guidelines: "The following are levels of concern at which the reviewer shall exercise appropriate actions to ensure that the safety of the device is substantially equivalent to a predicate device: A) If SAR 0.4 W/kg whole body; and if SAR 8.0 W/kg spatial peak in any 1 gram of tissue; and if SAR 3.2 W/kg averaged over the head: **below level of concern**. Or B) If exposure to radiofrequency magnetic fields is insufficient to produce a core temperature increase in excess of 1°C and localized heating to greater than 38°C in the head, 39°C in the trunk and 40°C in the extremities: **below level of concern**. The parameter SAR cited above must be shown to fall below either of the two levels of concern by presentation of valid scientific measurement or calculation evidence sufficient to demonstrate that SAR is of no concern."

It should be noted that this guideline is based on the calculation of a system that has no thermoregulatory response, and thus it is a very conservative estimate compared with the temperature change that would be experienced in any living subject. Normal diurnal temperature variations in humans, for example, are about +/-1°C from the normal set point 37°C, and healthy people with normal thermoregulatory responses can easily dissipate any excess (or, in this instance, deposited) heat by increasing their peripheral blood flow or sweat rate. Thus, the heating effect of MRI with the SARs used in accord with these guidelines is extraordinarily unlikely to cause any acute effects in healthy human subjects. Furthermore, our scanner console calculates SAR based on the subject's body weight before running any pulse sequence and prohibits running of the sequence if exceeds the FDA-approved limit.

Summary: Because all experiments performed on the 3.0 Tesla system will comply with FDA guidelines with regard to SAR, and because appropriate RF power safety checks are in place, this criterion for classification of NSR is satisfied.

d. Static Magnetic Fields: The possible risks of static magnetic fields have received much attention in the lay press, but scientific consensus on these risks has yet to be fully reached. The FDA has deemed that systems operating at 8.0 Tesla or less do not pose a significant risk. Moreover, experience with thousands of clinical studies over the past decade, and with multiple human investigations carried out at higher field strengths over this period, have not revealed risks of exposure to higher static magnetic fields. The most significant risk associated with static magnetic fields is that ferromagnetic objects, such as aneurysm clips or heart valves, can interact with the magnetic field of an MRI scanner, causing the device to malfunction or to move, and injuring the subject.

FDA Guidelines: "Studies conducted at 8T or less are not considered significant risk" (FDA Center for Devices and Radiological Health, memorandum 7-14-03).

Summary: This category of risk applies to work conducted around superconducting magnets of any kind (including standard clinical diagnostic MRI units). It is not unique to our 3.0 Tesla facility, which will maintain a safety policy to safeguard subjects and staff members from these incidental risks. Systems with static magnetic field less than 8 Tesla have been considered to represent a nonsignificant risk by the FDA. The static magnetic field of our system (3.0 Tesla) is therefore to be classified as posing NSR to human subjects.

d. Possible Incidental Risks: The physical confinement and isolation produced by the scanner could cause mild to moderate emotional distress, although in our extensive past experience, subjects generally tolerated the procedures remarkably well. Pregnant subjects will be excluded from participating in this study because of the unknown risk of MRI scans to the fetus. All female subjects will be given a urine pregnancy test on the day of the MRI scan. If the pregnancy test is positive, the subject will be excluded from further participation and encouraged to consult with their primary physician or family planning clinic. Appropriate referrals

will be made upon request.

Protecting Against Potential Risks As described above, subjects are safeguarded from undue risk by procedures to obtain informed consent, insure confidentiality, and minimize possible risks associated with the study. Described above are also the potential risks of the research procedures and specific measures to minimize each of those risks. Described below are general safeguards that will be used to minimize risks. These include exclusion of subjects at highest risk, the monitoring of any side effects, and the termination of subjects from research participation if it is believed that such participation endangers their welfare.

1) Careful medical and psychiatric screening to identify patients whose risk for potential adverse effects would be elevated with study procedures. Such patients will be excluded from the study. As an example, an actively suicidal patient would be excluded from study participation and referred for appropriate treatment. In addition, pregnant subjects will be excluded.

2) Careful monitoring of patients during the assessment and study period. Psychiatrists in the inpatient units at the NYSPI carry beepers and are available 24 hours per day for clinical emergencies.

3) Patients who begin the study and experience adverse effects sufficient to require removal from the study will be referred for appropriate clinical care. The exact nature of "appropriate clinical care" will be determined by the judgment of clinicians familiar with the specific patient and may include medication, cognitive-behavioral therapy, or other modalities.

4) As in any type of research, patients' confidentiality must be carefully guarded and respected. All data with identifying information will be stored in locked file cabinets or password-protected computer files. Data being analyzed will be identified by subject codes and identifying information will be removed. The identity of patients will not be revealed in the presentation or publication of any results from the project. All individuals working on the project will be educated about the importance of strictly respecting patients' rights to confidentiality.

5) To minimize the risk of being off of medication, no patients will be tapered off of medications solely for research purposes. Inclusion in the study will be limited to individuals who are between the ages of 18-55. For patients who will have their medications tapered during this study, a number of procedures will be in place in order to minimize the risks associated with being off of medications. First, medication tapers will only occur on inpatient units. In addition, treatment during the medication taper and medication free period will be a robustly collaborate effort, led by the inpatient attending physicians with close collaboration by the physicians in the Division of Translational Imaging (Drs. Abi-Dargham, Gil, Kegeles, Urban, and Girgis), who have a combined 45 years of experience with medication tapers in patients with schizophrenia in the context of research studies, and outpatient psychiatrists for the patients. Any patient who requests to be re-started on antipsychotic medication will be exited from the antipsychotic-free study period. Medication will also be restarted if any of the following Criteria for Clinical deterioration are met: (1) observed or reported aggressive/self-injurious behavior; (2) agitation; or (3) significant subjective distress/discomfort; or (4) CGI score of 6 or 7 during antipsychotic free period. Patients will also be exited from the protocol at any time if any of the patients, outpatient psychiatrists, inpatient attendings, or study physicians feel that the patient's clinical status is significantly worsening.

Additionally, throughout their inpatient stays, patients will be provided active and comprehensive non-pharmacologic treatment is provided. The unit provides active individual, group, and family psychoeducation programming which mitigates the risks of being off medications. In addition, PO lorazepam will be utilized as needed (up to a maximum of 8mg). For those patients who are already medication free, procedures will be maximized to ensure that there is less than 7-10 days between consent and treatment. For patients who require a medication taper and 3 week mediation-free period, every effort will be made to make sure that

the PET scanning can occur as close to the 3 week medication-free mark in order to minimize the medication free period. For all patients, no patients who are clinically unstable will be recruited into this protocol, on or off of medications. No patients who are already admitted as inpatients for clinical reasons or require an inpatient admission for an acute decompensation will be recruited into this protocol. No patients who have a history of severe criminality, violence, suicidality, or extreme distress while psychotic will be recruited into this protocol.

6) Our 3.0 Tesla scanner satisfies FDA criteria for nonsignificant risk (NSR) in all risk categories:

a. Acoustic Noise: As suggested by the FDA, we will take steps to reduce or alleviate the noise levels experienced by subjects in this protocol. The easiest and most reliable means of preventing hearing loss is to use disposable earplugs, which we intend to do for all scans. We will also be using acoustically shielded headsets, which further attenuate noise.

b. Nerve Stimulation: All consent forms for studies that might induce peripheral nerve stimulation also will provide this information. A record of dB/dt value will also be included with the imaging data to help in analysis of levels of peripheral nerve stimulation possibly perceived by subjects. In addition, we will conduct detailed calculations of the changes in magnetic field over time that our gradient system is capable of, and conservative values will be selected as limits that will be used to determine when special additional monitoring is indicated. In these cases, we will use the monitoring procedures recommended by the FDA. The gradient switching times and strengths will also be monitored together with the routine assessment of all electrical components of the system, as described previously. MR technologists will also receive special training to prevent peripheral nerve stimulation and before any scanning procedure that might stimulate peripheral nerves, a technologist will:

- Inform the subject that peripheral nerve stimulation may occur
- Describe the nature of the sensation to the subject
- Instruct subjects not to clasp their hands, since this may create a conductive loop which will increase the possibility of stimulation
- Maintain constant verbal contact with the subject
- Instruct subjects to inform the MR technologist if they experience discomfort or pain
- Terminate the scan if the subject complains of discomfort or pain
- Complete a report of any incidents involving severe discomfort or pain, including a description of the associated circumstances (imaging parameters, dB/dt value, level of pain, etc.), and submit this report immediately to the IRB.

c. Specific Absorption Rate: The magnitude of temperature increase during MRI scanning is minimal. Increases are always within FDA guidelines, which include core temperature increases less than 1°C, as well as localized heating to less than 38°C in the head, 39°C in the trunk, and 40°C in the extremities. Our 3.0 Tesla system has in place a means to monitor RF power levels and ensure that energy deposition is sufficiently low to stay well within these guidelines for temperature increases. First, a "system security" unit is employed to integrate the output of the RF amplifiers. This integration takes into account the amplitudes and duty cycle of the transmitter. If the system security detects an output that might exceed the guidelines noted above, it automatically shuts down the entire RF power system. Secondly, all pulse sequences are evaluated, based on calculations and sound scientific measurements, to ensure that SAR remains within FDA-approved guidelines, prior to their use in humans. Any experiment performed on our 3.0 Tesla system will comply with all FDA guidelines with regard to RF power deposition. Proper and routine monitoring of all RF electronics (e.g., coils, transmitters, system security, etc.) will be performed on a regular basis. All pulse sequences will be evaluated (by calculation and by valid scientific measurement) prior to use in humans.

d. Static Magnetic Fields: The minimization of risks associated with the static magnetic field of 3.0 Tesla is mainly related to incidental risks (see below). These risks are the same as in

other commercially available clinical systems. Consistent with clinical MRI centers, our facility incorporates a complete range of procedures to avoid inadvertent exposure of persons to the static field. We ensure security of the restricted access area with automatic locking doors, meticulous screening of potential subjects before they enter the restricted access area, and a positioning of a metal detector at the doorway leading into the magnet room within the MRI suite. Access to the MRI suite is tightly controlled, allowing access for only personnel and research subjects who have legitimate reason to be there. Doors to the unit are securely locked, with only MR technologists, physicists, or physicians controlling entry of ferromagnetic and other materials that could possibly cause injury to patients, research subjects, personnel, or equipment. In addition, entry-ways to the unit will be labeled with clear visible signs warning of the presence of the magnetic field and the exclusion from entry by individuals with implanted metal objects such as protheses, pins, clips, and IUD's.

e. Incidental MRI Risks All subjects will be able to communicate directly with technologists and study staff to inform them of any emotional or physical distress during the scanning procedure. If they wish, the scan will be terminated immediately and the subject will be removed from the scanner. Additionally, subjects will be instructed that they are free to stop the behavioral testing sessions at any time they wish. All subjects will be offered the opportunity to undergo a desensitization procedure and relaxation training in a mock scanner prior to having their MRI scan. These procedures minimize any potential anxiety the subjects may have concerning MRI scan, and they also help to acquire motion-free imaging data.

Risk/Benefit Ratio The MRI findings are unlikely to be of direct benefit to any of the subjects. The indirect benefit is the detailed knowledge that the study will provide about disturbances in neural systems that likely contribute to the development of psychotic symptoms, specifically hallucinations. Such knowledge will have an important positive impact because these neural disturbances may represent biomarkers that can aid in the identification, diagnosis, and, ultimately, the treatment of schizophrenia. Subjects will be informed of any clinically significant findings from the MRI and clinical assessments. Participation at each time point will be completed on 1 day. The diagnostic assessments (~2 hours), the MRI scan (~2 hours), and the neuropsychological testing (~1 hour) will take approximately a total of 5 hours to complete each study visit. Participants will receive a monetary compensation of \$120 for their participation. Treatment-seeking patients will be offered treatment in the Lieber Research Schizophrenia Clinic (NYSPI). Travel and parking expenses will be covered. The risks of participating in this study are negligible, especially in relation to the benefit and public health importance of understanding the neurobiological basis of psychosis and schizophrenia.

INCLUSION OF WOMEN AND MINORITIES

We will recruit approximately 50% female and 50% male participants. Based on our previous enrollment into studies in the Lieber Schizophrenia Research Clinic and the Brain Imaging Laboratory, we expect the subject distribution to be approximately 12% Hispanic or Latino, 71% White (not Hispanic or Latino), 15% Black, and 2% Asian. Because of our location in New York City, we do not anticipate problems recruiting ethnic or racial minorities. Our outreach efforts to recruit minorities include advertising in local newspapers in minority-rich neighborhoods, publicizing the study in local clinics treating large numbers of minority patients, and educating minority community groups about the availability of the study. In attempt to enhance minority recruitment, we will institute the below recruitment plan.

Minority Recruitment Plan Participants will be recruited from the organizations and clinics in the Northern Manhattan area. The Columbia site's facility is well located for recruitment of under-represented clinical populations. Outreach efforts will be made to organizations in the largely Hispanic neighborhood surrounding the hospital. To promote recruitment of minority subjects, we will advertise the study in medical clinics serving large numbers of minority individuals.

Targeted/Planned Enrollment Table**This report format should NOT be used for data collection from study participants.****Study Title:** "Neural mechanisms of sensory predictions in schizophrenia with hallucinations"**Total Planned Enrollment:** 60

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	4	3	7
Not Hispanic or Latino	26	27	53
Ethnic Category: Total of All Subjects*	30	30	60
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	5	9
White	25	25	50
Racial Categories: Total of All Subjects*	30	30	60

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

INCLUSION OF CHILDREN

Children (under 18 years old) will not be included in this study because childhood-onset schizophrenia is a rare form of the disorder. Due to the low incidence of schizophrenia in children, an extraordinary effort would be needed to include children with this disorder. In addition, due to the study design and its focus on auditory hallucinations, it is preferable to recruit patients over 18 years old who have a relatively long history of hallucinations and enough awareness into the illness to be able to provide clear reports on this symptom. Also, children would be expected to be at different cognitive stages to adults, so a separate study in children with a more suitable design for this population would be preferred.