

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

		<b>3. DATE RECEIVED BY STATE</b>	State Application Identifier
<b>1. TYPE OF SUBMISSION*</b>		4.a. Federal Identifier MH109836	
<input type="radio"/> Pre-application <input type="radio"/> Application <input checked="" type="radio"/> Changed/Corrected Application		<b>b. Agency Routing Number</b>	
<b>2. DATE SUBMITTED</b> 2016-03-11	<b>Application Identifier</b> PD/2016/01027	<b>c. Previous Grants.gov Tracking Number</b> GRANT12118232	
<b>5. APPLICANT INFORMATION</b>			Organizational DUNS*: 1672049940000
Legal Name*:	Research Foundation for Mental Hygiene, Inc.		
Department:	110 NYPI Child and Adolescent		
Division:			
Street1*:	NYPI		
Street2:	1051 Riverside Dr		
City*:	New York		
County:	New York		
State*:	NY: New York		
Province:			
Country*:	USA: UNITED STATES		
ZIP / Postal Code*:	10032-1007		
Person to be contacted on matters involving this application			
Prefix: Ms.	First Name*:	Janelle	Middle Name: Rene
Position/Title:	Last Name*: Greenhill Suffix: MPH		
Street1*:	Director of Administration		
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Phone Number*:	646-774-6500	Fax Number:	646-774-6540 Email: nga@nyspi.columbia.edu
<b>6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)*</b>		1141410842A2	
<b>7. TYPE OF APPLICANT*</b>		M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)	
Other (Specify):			
Small Business Organization Type		<input type="radio"/> Women Owned	<input type="radio"/> Socially and Economically Disadvantaged
<b>8. TYPE OF APPLICATION*</b>		If Revision, mark appropriate box(es).	
<input type="radio"/> New	<input checked="" type="radio"/> Resubmission	<input type="radio"/> A. Increase Award	<input type="radio"/> B. Decrease Award
<input type="radio"/> Renewal	<input type="radio"/> Continuation	<input type="radio"/> C. Increase Duration	<input type="radio"/> D. Decrease Duration
		<input type="radio"/> E. Other (specify):	
Is this application being submitted to other agencies?*		<input type="radio"/> Yes	<input checked="" type="radio"/> No
What other Agencies?			
<b>9. NAME OF FEDERAL AGENCY*</b> National Institutes of Health		<b>10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER</b> TITLE:	
<b>11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*</b> Neural Correlates of Fear Over-Generalization in Youth with Pathological Anxiety			
<b>12. PROPOSED PROJECT</b> Start Date* 09/01/2016		<b>13. CONGRESSIONAL DISTRICTS OF APPLICANT</b> Ending Date* 08/31/2020	

**SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE****14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

Prefix: Dr. First Name\*: Jiook Middle Name: Last Name\*: Cha Suffix:  
 Position/Title: Research Scientist  
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 Phone Number\*: 646-774-5877 Fax Number: Email\*: chajoo@nyspi.columbia.edu

**15. ESTIMATED PROJECT FUNDING**

a. Total Federal Funds Requested*	\$740,876.00
b. Total Non-Federal Funds*	\$0.00
c. Total Federal & Non-Federal Funds*	\$740,876.00
d. Estimated Program Income*	\$0.00

**16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?\***

- a. YES  THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:  
 DATE:
- b. NO  PROGRAM IS NOT COVERED BY E.O. 12372; OR  
 PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

**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)**

I agree\*

\* 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.

**18. SFLLL or OTHER EXPLANATORY DOCUMENTATION**

File Name:

**19. AUTHORIZED REPRESENTATIVE**

Prefix: Ms. First Name\*: Janelle Middle Name: Rene Last Name\*: Greenhill Suffix: MPH  
 Position/Title\*: Director of Administration  
 Organization Name\*: Research Foundation for Mental Hygiene, Inc.  
 Department: 110 NYPI Facilities and Admini  
 Division:  
 Street1\*: NYPI  
 Street2: 1051 Riverside Dr  
 City\*: New York  
 County: New York  
 State\*: NY: New York  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 10032-1007  
 Phone Number\*: 646-774-6500 Fax Number: 646-774-6540 Email\*: nga@nyspi.columbia.edu

**Signature of Authorized Representative\***

Ms. Janelle Rene Greenhill MPH

**Date Signed\***

03/14/2016

**20. PRE-APPLICATION** File Name:**21. COVER LETTER ATTACHMENT** File Name:0 Cover Letter\_FINAL\_1.pdf

## 424 R&R and PHS-398 Specific Table Of Contents

Page Numbers

SF 424 R&R Cover Page-----	1
Table of Contents-----	3
Performance Sites-----	4
Research & Related Other Project Information-----	5
Project Summary/Abstract(Description)-----	6
Project Narrative-----	7
Bibliography & References Cited-----	8
Facilities & Other Resources-----	14
Other Attachments-----	19
0 List of Referees-----	19
Research & Related Senior/Key Person-----	20
Research & Related Budget Year - 1-----	63
Research & Related Budget Year - 2-----	66
Research & Related Budget Year - 3-----	69
Research & Related Budget Year - 4-----	72
Budget Justification-----	75
Research & Related Cumulative Budget-----	80
PHS398 Cover Page Supplement-----	81
PHS 398 Career Development Award-----	83
Introduction To Application-----	84
Candidate Background-----	85
Career Goals and Objectives-----	87
Career Development and Training Activities-----	88
Responsible Conduct Of Research-----	92
Statements of Support-----	93
Letters of Support-----	98
Institutional Environment-----	103
Institutional Commitment-----	104
Specific Aims-----	105
Research Strategy-----	106
Protection of Human Subjects-----	114
Inclusion of Women and Minorities-----	120
Planned Enrollment Report-----	121
Inclusion of Children-----	122

**Appendix**

Number of Attachments in Appendix: 1

## 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\*: 10032-1007  
Project/Performance Site Congressional District\*: NY-013

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File Name

**Additional Location(s)**

## RESEARCH &amp; 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: 02-05-2015

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?

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 the United States or partnership with international collaborators?\***  Yes  No

6.a. If yes, identify countries:

6.b. Optional Explanation:

Filename

**7. Project Summary/Abstract\*** FINAL.pdf**8. Project Narrative\*** FINAL\_2.pdf**9. Bibliography & References Cited** REFERENCES\_1459.pdf**10. Facilities & Other Resources** FINAL1520.pdf**11. Equipment****12. Other Attachments** 0 List of Referees.pdf

## PROJECT SUMMARY

Anxiety disorders, as a group, are the most common mental illnesses in the US, affecting about 25% of adolescents and 18% of adults. Symptoms typically begin in childhood or adolescence. A crucial gap in studies of anxiety is the lack of empirical data linking pediatric anxiety to abnormal brain development. This four-year K01 application presents a program for research and training that will support the applicant on a path towards becoming an NIH-funded independent investigator, focused on studying the neural correlates of fear generalization in youth with pathological anxiety using interdisciplinary approaches (affective neuroscience, multimodal neuroimaging, and computational methods). The training plan builds on the candidate's previous training and experience, and capitalizes on a mentorship team and a research environment to foster development of the candidate's expertise in (1) the phenomenology of anxiety disorders; (2) patient-oriented, translational and developmental neuroscience of anxiety; (3) advanced computational neuroimaging; and (4) responsible and ethical conduct in scientific research in vulnerable individuals. The research project will investigate fear generalization behavior and its relationship with vmPFC (ventromedial prefrontal cortex) function and corticolimbic connectivity in healthy youth (Aim #1), and investigate fear over-generalization behavior and its relationship with vmPFC function and corticolimbic connectivity in youth with pathological anxiety (Aim #2). We hypothesize that childhood anxiety involves fear over-generalization and that fear over-generalization involves abnormal function and connectivity of the corticolimbic system. To test these hypotheses, we will use a fear generalization fMRI task and multimodal MRI (structural, diffusion, and functional MRI) in healthy youth without anxiety ( $n=25$ ) as well as in youth with pathological anxiety across a spectrum of severity (i.e., those with subthreshold anxiety [ $n=25$ ] and those with any DSM-5 anxiety disorder [ $n=25$ ]). Successful completion of this study will provide cross-sectional evidence of the association of pediatric anxiety with fear generalization behavior, vmPFC function, and corticolimbic system connectivity. The multiple units of analysis will help elucidate brain-behavior relationships underlying fear generalization. These data along with the research expertise developed through this K01 award will support a future R01 application to track over time the developmental trajectories of fear generalization and pathological anxiety in youth. The ultimate goal of this line of research is to develop neurobehavioral markers to determine when and where to intervene in anxiety disorders (*NIMH Strategic Objective 2*) and to promote preventive therapeutic interventions to youth with pathological anxiety (*NIMH Strategic Objective 3*).

## **PROJECT NARRATIVE**

Anxiety disorders in youth are very common and presage the development of other debilitating diseases, such as depression and substance abuse. In this proposal, we will test whether anxious youth show over-generalization to stimuli conditioned to fear, and to examine the related neural circuitry. Results from this study could lead to the development of new targets for treatment development as well as strategies to prevent the onset of anxiety disorders.

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## FACILITIES AND OTHER RESOURCES

### Overview

The combined imaging study to investigate over-generalization of fear in pediatric anxiety will be conducted within the Division of Child & Adolescent Psychiatry at Columbia University (CU) and New York State Psychiatric Institute (NYSPI), both on the campus of the Columbia University Medical Center (CUMC). The facilities and other resources available to this investigative team include everything needed to undertake and complete the proposed project successfully. The collaboration between Drs Cha, Posner, and Simpson, who are experts in systems neuroscience, pediatric neuroimaging, and translational neuroscience, respectively, represents a realization of the emphasis on collaborative, translational neuroscience research that is central to the Division of Child & Adolescent Psychiatry at Columbia University.

### **1. How the Scientific Environment Contributes to the Probability of Success**

Dr Jiook Cha, the project's PI has extensive evidence of institutional commitment to his development as an academic researcher. Dr Cha has *laboratory space* in Dr. Posner's laboratory, access to *equipment* for this project (e.g., psychophysiology data acquisition system for behavioral testing), and access to *clinical resources* to recruit adolescents as evidenced by the preliminary data for this K01 application. Dr Cha's access to the *imaging resources* in the Department of Psychiatry and the *computational resources* (e.g., High-Performance Computing (HPC) "supercomputer" Systems) at CU is also evidenced by his recent MRI study in children with ADHD<sup>13</sup>. These imaging data were acquired on the 3 Tesla MRI scanner that will be used for the proposed study. The rich clinical research environment described in detail below will ensure participants recruitment, data acquisition and analysis, and ultimately contribute to the study's success.

### **2. Clinical Resources**

**New York State Psychiatric Institute:** New York State Psychiatric Institute (NYSPI), a facility within the New York Office of Mental Health system, has been one of the world's leading institutions for psychiatric research for more than 100 years. NYSPI is renowned for its psychiatric research, its training and educational resources, and its clinical care, housing inpatient services and research units as well as 23 outpatient research units. Its resources, research faculty, and staff, combined with those of the Research Foundation for Mental Hygiene's Division at NYSPI and the Columbia University Department of Psychiatry, have made the NYSPI one of the nation's most respected psychiatric research centers. It comprises two entire buildings as well as several floors of a third building.

**New York Presbyterian Hospital at Columbia University Medical Center:** Columbia University Medical Center's (CUMC) affiliated hospital, New York-Presbyterian Hospital (NYPH) was ranked first among New York hospitals by *U.S. News and World Report*; it placed on the *U.S. News and World Report* Honor Roll as one of the 17 best hospitals in the United States. Research institutes and centers based at the CUMC campus include the Center for Community Health, the Howard Hughes Medical Institute Program, the Center for the Study of Society and Medicine, the Center for Medical Informatics, and the Columbia Genome Center.

**Pediatric Anxiety and Mood Research Clinic (PAMRC, directed by Dr. Moira Rynn, an advisor):** PAMRC is a specialty research clinic dedicated to improving the lives of children and adolescents suffering from anxiety and mood disorders. Directed by Dr. Moira Rynn, PAMRC is part of the Department of Psychiatry at Columbia University and is located in Washington Heights, New York City. PAMRC provides comprehensive evaluations, treatment with evidence-based therapy and medications, and a day treatment program with academic services for youth requiring intensive care. All assessment and treatment services at PAMRC are free of charge. PAMRC sees over 100 new adolescents (ages of 13-17) referred for anxiety disorders per year.

**Children's Day Unit (directed by Dr. Moira Rynn, an advisor):** The Children's Day Unit (CDU) is an outpatient day hospital program, directed by Dr. Moira Rynn, located at the New York State Psychiatric Institute/Columbia University Medical Center. The CDU is comprised of research participants and adolescents ages 13 to 17 years from the community who require intensive outpatient care. The CDU specializes in the treatment of Generalized Anxiety Disorder, Social Phobia, Post-Traumatic Stress Disorder, Obsessive-Compulsive Disorder, Depression, and other psychological disorders. All adolescents attending the CDU receive a comprehensive evaluation and then enter a structured therapeutic program. During the academic year, the CDU partners with the New York City Board of Education to provide education for students through the public school (PS 186X) located on the unit. Students attend class daily and are often eligible to earn school credits while attending the CDU.

**Children's Anxiety & Depression Clinic at Children's Hospital of New York at Presbyterian Medical Center (CHONY):** Under the direction of Warren Ng, MD, the Child Psychiatry Outpatient Service at the Children's Hospital of New York (CHONY) is a group of specialized subclinics, including a pediatric anxiety clinic, that handle approximately 34,000 patients annually. Clinicians from the clinic regularly consult with child psychiatry research faculty to ensure that patients are provided the most-up-to-date psychopharmacological and psychotherapeutic treatment. Drs. Posner (mentor) and Rynn (advisor) have worked closely with staff to recruit research participants in this clinic. Dr. Rynn also provides consultation to this clinic. In 2014, 300 distinct adolescents (ages of 13-17) were referred for an anxiety disorder without other (e.g., depressive) disorders.

**Columbia University Clinic for Anxiety and Related Disorders (CUCARD)** at CU/NYSPI: CUCARD, under the direction of Dr. Anne-Marie Albano, is a specialty clinic in the Division of Child & Adolescent Psychiatry of Columbia University. This clinic specializes in delivering empirically-supported cognitive-behavioral therapies for children, adolescents, and young adults suffering from anxiety or anxiety-related disorders. This clinic is committed to translating the latest in scientific findings about what works best for children and adolescent patients with anxiety and related disorders, and providing the patients with care that gives the best chance of recovery. Dr. Rynn (advisor) is the medical director for CUCARD and Dr. Simpson (co-mentor) serves as consultant for this clinic. This clinic sees 200 new adolescents (ages of 13-17) referred for anxiety disorders per year.

**ResearchMatch®:** CU/NYSPI is participating in this free national research participant registry, created and is managed by Vanderbilt University. The purpose of the system is to match individuals who are willing to participate in research with researchers who need volunteers for their studies. ResearchMatch® is available to help match any type of IRB-approved study with potential volunteers. As of 2016, more than 90,000 research volunteers have been recruited in the US.

### **3. Laboratory and Scanning Facilities**

**Data Acquisition and Analysis System Psychophysiology Research:** Dr. Posner's lab is equipped with AcqKnowledge® and BIOPAC® MP36R 4-Channel Systems with built-in universal amplifiers (Biopac Systems, Inc, Goleta, CA) to collect and analyze psychophysiological data. This system provides high resolution, variable sample rates for analog and calculation channels, analog inputs and outputs, digital I/O lines, and online calculation channels. AcqKnowledge® will be synced with a task presentation program (Presentation®, Neurobehavioral Systems, Inc, Berkeley, CA) to collect time-locked physiological data in the behavioral experiment. The MRI unit is equipped with the equivalent BIOPAC system that is MR-compatible. During the fear generalization task, this system will be used to collect Skin Conductance Resistance (SCR), heart rate, and skin temperature.

**NYSPI and CU Department of Psychiatry 3.0 Tesla MRI Laboratory:** The NYPSI MRI unit is the location of a General Electric (GE) 3.0 Tesla (T) high-performance MRI scanner. The site is state-of-the-art for image acquisition and analysis:

**MRI Scanning Suite:** NYSPI's GE 3.0 T whole-body scanner resides within a 3,200 square-foot 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 radio frequency coils, a subject "on-deck" 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 MRI physicist, and a viewing room. The suite is equipped with 3 Hewlett Packard (HP) xw8000 workstations with full-image processing capabilities for all MRI modalities, one HP LaserJet 1320n color printer, two Sun Ultra 60 workstations, and six Pentium 4 class PC's, each with a 3GHz CPU, 2GB RAM, and 200GB or more of 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 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 within NYSPI occurs over a dedicated fiber optic network (with data transfer rate of 1 Gb/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 (e.g., e-mail or other end-user applications) and will avoid burdening a Local Area Network (LAN) with data storage, retrieval, and archival activities.

**Whole Body 3.0 Tesla MRI Scanner:** The Signa 3.0 Tesla magnet, with a 55 cm 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 (< 0.05 ppm on water spectral FWHM for 20 cm DSV), which is essential for good image quality in demanding techniques such as spectroscopy and ultrafast 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 ultrahigh spatial resolution (0.1 mm slice thickness in 3D) and ultrafast imaging (34.0 ms TR for 64 x 64 matrix EPI). Furthermore, 14 passive superconducting shim coils improve the main field homogeneity up to < 0.1 ppm 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 ultralow-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 32-channel HDx hardware platform, the EXCITE 3.0T head coils, and 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 2.66 GHz processors with 2GB host memory linked to an EXCITE vector array processor make simultaneous computing technology possible (400 images/sec for 256 x 256 FFT), thereby benefiting real-time interactive imaging.

**RF Coil Laboratory:** A design laboratory in the NYSPI MRI Unit houses electronic device building and repair. It consists of 400 square feet with bench space and tool storage, equipped with electronics (e.g., voltmeters, oscilloscopes, circuit design and construction). 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 multivoxel (3D chemical shift imaging; i.e., CSI) basis. A multinuclear 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 (e.g., PROBE2000, PROBE 3D Brain, FuncTool, spiral, diffusion, fast spin echo, and Brain Wave packages). These permit easy visualization of single-voxel and multivoxel spectra MRS data, 2D and 3D chemical shift imaging, parametric metabolite mapping, diffusion tensor post processing, and functional brain mapping (BOLD), as well as fMRI stimulus sequencing and presentation.

**MR Image Processing Laboratory:** This is directly above the MRI scanning suite at NYSPI, where it occupies more than 2000 square feet. The imaging laboratory currently has one Sun Ultra 1, seven Sun Ultra 10, and two Sun Ultra 60 workstations, each with 512 MB RAM, dual 300-450 MHz SPARC-V9 floating point processors, 19-inch LCD color monitors, eight 75GB external hard drives for data storage, and an external optical drive. We also have two Sun Fire V880 servers with dual 900 and 1200 MHz CPUs, 4GB RAM, and 850 GB RAID 5 hard disk storage, along with an integrated fiber channel subsystem that provides an I/O performance of 1.2 GB/sec. Additionally, two Dell PowerEdge 6600 servers with four CPUs, 6 GB RAM, and 600GB disk space, running Microsoft Windows Server 2003, provides computing power and memory to even the most demanding image processing methods. From SAN to the servers, 4.5 TB high-speed disk array are connected via 2 Gbps fiber channels. A Network-Attached Storage (NAS) with 3.75 TB high-speed SCSI disk array is used for daily backup. A 1.9 TB tape library is also attached to the Dell server to perform monthly backup.

The lab also has two state-of-the-art Silicon Graphics workstations, 10 dual-processor Pentium 4 PCs with 3.4GHz CPUs, 3GB RAM, and 500GB hard disks, 12 Pentium PC's, three Dell Inspiron Pentium laptops, two Macintosh laptops, five external optical drives, an HP LaserJet 4700dn color printer, an HP LaserJet 4250dn laser printer, an HP LaserJet 4100dn laser printer, a Lexmark C910 color printer, and a Seiko Colorpoint 860 color printer.

These workstations are seamlessly interconnected on the LAN to provide a distributed computing environment for the most efficient use of computing power and storage space by research assistants. 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.

Although the Image Processing Lab at NYSPI has extensive experience conducting structural MRI research, the laboratory uses manual techniques and analytic software that are not available to investigators outside of that laboratory. Dr. Cha has extensive experience analyzing structural MRI data using Freesurfer (<http://surfer.nmr.mgh.harvard.edu/>; see 12. Research Strategy—C1. Preliminary Studies). Freesurfer uses an automated algorithm for subcortical brain segmentation, is widely accepted in the imaging community, and is freely available to all investigators. Developing expertise in this approach to structural MRI research rather than the manual approach of the NYSPI Image Processing Lab will allow Dr Cha to become a fully independent investigator.

#### **4. Computational and Biostatistical Resources**

**High-Performance Computing (HPC) Systems:** Columbia University's Advanced Research Computing Services (ARCS) maintains several high-performance computing systems, including multiple high-performance computing clusters as well as high-memory systems. In 2013 a new cluster with 6,336 CPU-cores and 73,728 CUDA-cores (GPU) replaced the previous Titan system. The new system has a maximum performance of 212 TFlops, almost nine times the performance of its predecessor. The system is on the Top 500 list of supercomputers worldwide.

The new system has a number of improvements over the current system, including 10 Gbps Ethernet fabric throughout, 40 Gbps QDR InfiniBand for a portion of the system, GPU-enhanced computing, and a new, lower power hardware architecture. All of the clusters run current variants of the Linux operating systems, and are managed by Univa Grid Engine. Additionally, ARCS has two high-memory systems with 1 TB of system memory each, and a pool of computational servers for compilation, debugging, and job control.

The HPC system has most of the widely used neuroimaging data analysis pipelines (e.g., FSL [Functional MRI of the Brain Software Library], Freesurfer, SPM, AFNI) and other data analysis software (e.g., MATLAB). Using these, Dr. Cha has previously run diffusion probabilistic tractography analyses in a recent childhood ADHD study<sup>13</sup> and currently runs the majority of neuroimaging data analysis.

**The Department of Biostatistics at Columbia University's (CU) Mailman School of Public Health** 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 New York State Psychiatric Institute (NYSPI) researchers to help them answer their research questions. Chair of the Department of Biostatistics, **Dr. Bowman (consultant, advisor)** will provide consultation on biostatistical application in the research and training plans.

NYSPI's Biostatistics Division also 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 CU in methodological topics related to neuropsychiatric research, and providing consultations on data-analytic and design issues for grant submission and manuscript preparation.

#### **5. Computer Facilities**

All personal computers are linked to a printer and to the NYSPI and CU computer networks. The study has access to all network support made available by NYSPI and by its Division of Child Psychiatry. The network consists of three Novell servers and four Windows servers. These servers are used to share files, host Web sites, and run the e-mail system. The data and e-mail databases are backed up to tapes regularly. Tapes are rotated on a two-week cycle and the month-end tape is saved. Data up to two years old can be restored from tape.

#### **6. Office Facilities**

All faculty members have private offices at the NYSPI. Each office comprises roughly 200 square feet and is provided with a phone, a desktop computer, filing cabinets, and Internet connectivity. Three research assistants will share an office provided with phones, desktop computers, filing cabinets, and Internet connectivity.

## **7. Clinical Facilities**

### **Child Psychiatry Outpatient Service at Children's Hospital of New York at Presbyterian Medical Center:**

Under the direction of Lou Baptista, MD, the Child Psychiatry Outpatient Service at the Children's Hospital of New York (CHONY) is a group of specialized subclinics that handles approximately 34,000 patients annually. Clinicians from the clinic regularly consult with child psychiatry research faculty to ensure that patients are provided the most-up-to-date psychopharmacological and psychotherapeutic treatment.

## **8. Other Facilities**

Interview rooms can also be scheduled for assessment and treatment visits. A comfortable waiting room stacked with toys and magazines is available for families as they wait for their appointments. Rooms with one-way mirrors and a room equipped for videotaping are available to be scheduled on the Children's Day Unit, which is also on the second floor of the NYSPI–Herbert Pardes building.

## Referees

The following is a list of referees who have written letters of reference in support of Dr Jiook Cha's K01 Mentored Research Scientists Development Award:

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## RESEARCH &amp; RELATED Senior/Key Person Profile (Expanded)

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Project Role*: Other (Specify)	Other Project Role Category: Collaborator			
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name Biosketch_4_Dr Rynn_1.pdf			
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Daniel	Middle Name	Last Name*: Pine	Suffix:
Position/Title*:	Tenured Investigator; Branch Chief; Section C			
Organization Name*:	NIMH			
Department:	Section on Development and Aff			
Division:				
Street1*:	Building 15K, Room 110			
Street2:				
City*:	BETHESDA			
County:	USA			
State*:	MD: Maryland			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	20814-1234			
Phone Number*: 301 594 1318	Fax Number:	E-Mail*: pined@mail.nih.gov		
Credential, e.g., agency login:				
Project Role*: Other (Specify)	Other Project Role Category: Consultant			
Degree Type: MD	Degree Year:			
Attach Biographical Sketch*:	File Name Biosketch_5_Dr Pine_1.pdf			
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Dubios	Middle Name	Last Name*: Bowman	Suffix:
Position/Title*:	Professor and Chair of Biostatistics			
Organization Name*:	Columbia University			
Department:	Biostatistics			
Division:				
Street1*:	722 West 168th Street, Mail Code: 6th Floor			
Street2:				
City*:	NEW YORK			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	10032-1234			
Phone Number*:	212 342 4254	Fax Number:	E-Mail*: dubois.bowman@columbia.edu	
Credential, e.g., agency login:				
Project Role*:	Other (Specify)	Other Project Role Category: Collaborator		
Degree Type:	PHD	Degree Year:		
Attach Biographical Sketch*:	File Name Biosketch_6_Dr Bowman_1.pdf			
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Klaas	Middle Name	Last Name*: Stephan	Suffix:
Position/Title*:	Professor of Biomedical Engineering; Director			
Organization Name*:	ETH Zurich & University of Zurich			
Department:	Translational Neuromodeling Un			
Division:				
Street1*:	University of Zurich & ETH Zurich Institute for Biomed			
Street2:				
City*:	ZURICH			
County:				
State*:				
Province:				
Country*:	CHE: SWITZERLAND			
Zip / Postal Code*:	80320-1234			
Phone Number*:	41 44 634	Fax Number: 9111	E-Mail*: stephan@biomed.ee.ethz.ch	
Credential, e.g., agency login:				
Project Role*:	Other (Specify)	Other Project Role Category: Consultant		
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name Biosketch_7_Dr Stephan_1.pdf			
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Shinjae	Middle Name	Last Name*: Yoo	Suffix:
Position/Title*:	Associate Scientist			
Organization Name*:	Brookhaven National Laboratory			
Department:	Computational Science Center			
Division:				
Street1*:	Bldg. 463B - P.O. Box 5000			
Street2:				
City*:	UPTON			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	11973-5000			
Phone Number*:	6313445751	Fax Number:	E-Mail*: sjyoo@bnl.gov	
Credential, e.g., agency login:				
Project Role*:	Other (Specify)	Other Project Role Category: Consultant		
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name Biosketch_8_Dr Yoo_1.pdf			
Attach Current & Pending Support:				

**BIOGRAPHICAL SKETCH**

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

NAME: Jiook Cha

eRA COMMONS USER NAME (credential, e.g., agency login): JIOOKCHA

POSITION TITLE: Postdoctoral Research Fellow

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Korea University, Seoul, Korea	BS	02/2007	Environmental Engineering
Catholic Medical College, Seoul, Korea	MS	08/2009	Neurobiology
Stony Brook University, Stony Brook, NY	PhD	12/2013	Cognitive Neuroscience (Neuroimaging)
Columbia University, New York, NY	Fellow	02/2014	Psychiatric research (Pediatric neuroimaging)

**A. Personal Statement**

My long-term goal is to develop sensitive and specific neurobehavioral markers that can be ultimately used for early detection, intervention, and prevention of pathological anxiety in youth. To achieve this goal, the present K01 proposal will provide me with the research experience, training, and mentoring that will allow me to transition to become an independent investigator, studying the impact of anxiety on developmental trajectories of fear generalization and the neural systems. The following experience and qualifications make me well suited to receive this K01 award: (i) Training in interdisciplinary science, (ii) Research in fear generalization and pediatric neuroimaging, (iii) Track records of publications and awards, and (iv) Mentoring team for this K01 application.

- a) **Cha J**, Greenberg T, Carlson JM, Dedora D, Hajcak G, Mujica-Parodi LR (2014) Circuit-wide Structural and Functional Factors of Ventromedial Prefrontal Fear Response and Contribution to Anxiety Disorder. The Journal of Neuroscience; 34(11): 4043-4053.
- b) **Cha J**, Carlson JM, Dedora D, Greenberg T, Hajcak G, Mujica-Parodi LR (2014) Hyper-Reactive Human Ventral Tegmental Area and Aberrant Mesocorticolimbic Connectivity in Overgeneralization of Fear in Generalized Anxiety Disorder. The Journal of Neuroscience; 34(17): 5855-5860 (Feature Article).
- c) **Cha J**, DeDora D, Nedic S, Ide J, Greenberg T, Hajcak G, Mujica-Parodi LR. Clinically anxious patients show disrupted feedback between inferior frontal gyrus and prefrontal-limbic control circuit. The Journal of Neuroscience (in press).
- d) **Cha J**, Fekete T, Siciliano F, Biezonski D, Greenhill L, Pliszka SR, Blader JC, Roy AK, Leibenluft E, Posner J, Neural correlates of aggression in medication naïve children with ADHD: Multivariate analysis of morphometry and tractography. Neuropsychopharmacology 2015 Jun;40(7):1717-25.

**Explanation for lack of previous federal funding/fellowships.** During my PhD and postdoctoral training, I was ineligible to apply for federal grants or fellowships because of my citizenship status. I received US permanent residency in Dec 2015.

## B. POSITIONS AND HONORS

### Positions and Employment

- 2007-2009 Research Assistant, Department of Anatomy, Catholic Medical College, Seoul, Korea  
2010-2013 Research Assistant, Department of Neurobiology and Behavior, Stony Brook University, Stony Brook, NY  
2014- Postdoctoral Research Fellow, Division of Child and Adolescent, Department of Psychiatry, Columbia University, New York, NY  
2014- Research Scientist, The New York State Psychiatric Institute, New York, NY

### Other Experience and Professional Memberships

- 2008-2009 Member, Association for Research in Vision and Ophthalmology  
2012- Member, Society for Neuroscience  
2013- Member, Organization for Human Brain Mapping  
2014- Member, Society of Biological Psychiatry  
2015- Member, Anxiety and Depression Association of America  
2014- Ad-hoc reviewer, British Journal of Psychiatry, Psychological Medicine, Organization for Human Brain Mapping Annual Meeting

### Honors and Awards

- 2005 *College Specialization Project Scholarship* | Korea University, Seoul, Korea  
2007 *Korea Research Foundation Scholarship* | Korea Research Foundation, Seoul, Korea  
2008 *Best Abstract Travel Grant* | Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL  
2013 *Sigma Xi Award for Travel* | Stony Brook University, Stony Brook, NY  
2013 *Distinguished Travel Award* | Stony Brook University, Stony Brook, NY  
2014 *Outstanding Postdoctoral Research Award* | Association of Korean Neuroscientists at the Annual Meeting of Society for Neuroscience, Washington DC  
2015 *Career Development Travel Grant* | Anxiety and Depression Association of America, Miami, FL  
2015 *Career Development Leadership Program* | Anxiety and Depression Association of America, Miami, FL  
2015 *Travel Award* | Wisconsin Symposium on Emotion, Madison, WI

## C. CONTRIBUTION TO SCIENCE

1. **Fear Generalization.** I delineated neural circuits of fear **over**-generalization in adults. Building on these, I showed that the disrupted vmPFC threat processing in generalized anxiety disorder (GAD) involves an abnormal corticolimbic circuit. I also showed that an abnormally increased midbrain ventral tegmental area (VTA) involves fear over-generalization in GAD.
- a) **Cha J**, Greenberg T, Carlson JM, Dedora D, Hajcak G, Mujica-Parodi LR (2014) Circuit-wide Structural and Functional Factors of Ventromedial Prefrontal Fear Response and Contribution to Anxiety Disorder. *The Journal of Neuroscience*; 34(11): 4043-4053.
  - b) **Cha J**, Carlson JM, Dedora D, Greenberg T, Hajcak G, Mujica-Parodi LR (2014) Hyper-Reactive Human Ventral Tegmental Area and Aberrant Mesocorticolimbic Connectivity in Overgeneralization of Fear in Generalized Anxiety Disorder. *The Journal of Neuroscience*; 34(17): 5855-5860 (Feature Article).
  - c) **Cha J**, DeDora D, Nedic S, Ide J, Greenberg T, Hajcak G, Mujica-Parodi LR. Clinically anxious patients show disrupted feedback between inferior frontal gyrus and prefrontal-limbic control circuit. *The Journal of Neuroscience* (in press).
  - d) Greenberg T, Carlson JM, **Cha J**, Hajcak G, Mujica-Parodi LR (2013) Ventromedial prefrontal cortex reactivity is altered in generalized anxiety disorder during fear generalization. *Depression and Anxiety*; 30(3): 242-250.
2. **Attention Bias to Threat.** I identified neural circuits associated with attention bias to threat. Using a behavioral task (a dot-probe task) and MRI, I found that a greater attention bias correlates with connectivity between the amygdala and the PFC. Moreover, I found that amygdala-PFC connectivity mediates impact of the well-known genetic risk factor for anxiety, BDNF val66met SNP, on an attention bias. These studies provide novel evidence of gene-brain-behavior relationship underlying attention bias to threat in healthy adults.

- a) Carlson JM\*, **Cha J\***, Harmon-Jones E, Mujica-Parodi LR, Hajcak G (2014) Influence of the BDNF genotype on amygdalo-prefrontal white matter microstructure is linked to nonconscious attention bias to threat. *Cerebral Cortex*; 24(9): 2249-2257 (Feature Article).
- b) Carlson JM\*, **Cha J\***, Mujica-Parodi LR (2013) Functional and structural amygdala-anterior cingulate connectivity correlates with attentional bias to masked threat. *Cortex*; 49(9): 2595-2600.

**3. Prediction of Symptoms of Childhood Mental Disorders.** Early intervention is important in mental illnesses because brain abnormalities may begin long before onsets of the symptoms. For the early intervention, early detection of brain abnormality is crucial, yet not enough empirical data have existed to afford the establishing of reliable predictors. I demonstrated MRI-connectivity based prediction of symptoms of mental disorders. Using brain's reward connectivity from diffusion MRI and probabilistic tractography, multivariate pattern recognition analyses showed significant prediction of aggression in childhood ADHD (ages 8-12 years). In a Near-Infrared Spectroscopy study with toddlers (ages 3-5 years), measures of functional network (e.g., small-world properties) within the PFC correlate with 'effortful control', indicative of childhood psychopathology, such as anxiety, depression, and ADHD. These studies show feasibility and a promise of brain connectivity measures combined with computational approach to be used as an avenue to study psychopathology in children.

- a) **Cha J**, Fekete T, Siciliano F, Biezonski D, Greenhill L, Pliszka SR, Blader JC, Roy AK, Leibenluft E, Posner J, Neural correlates of aggression in medication naïve children with ADHD: Multivariate analysis of morphometry and tractography. *Neuropsychopharmacology* (In press)
- b) Fekete T, Beacher FD, **Cha J**, Rubin D, Mujica-Parodi LR (2014) Small-world network properties in pre-frontal cortex correlate with predictors of psychopathology risk in young children: a NIRS study. *Neuroimage*; 85 Pt 1: 345-353.

**4. Integration of Multimodal MRI for Structure-Function Relationship.** Impaired hippocampal function has been implicated in anxiety and depression, yet no empirical data for the 'common' neural substrate of anxiety and depression have been reported. In a recent study I have shown this relationship. I found atypical hippocampal grey matter integrity (using diffusion MRI) and atypical hippocampal threat processing associated with clinical anxiety. Using structural equation modeling I discovered that hippocampal threat processing mediates effects of hippocampal grey matter integrity on negative affects (i.e., anxiety and depression symptoms). Based on this work, I received the ADAA Career Development Travel Award and Travel Award of Wisconsin Symposium on Emotion.

- a) **Cha J**, Fekete T, Siciliano F, Biezonski D, Greenhill L, Pliszka SR, Blader JC, Roy AK, Leibenluft E, Posner J, Neural correlates of aggression in medication naïve children with ADHD: Multivariate analysis of morphometry and tractography. *Neuropsychopharmacology* (In press)

- **Complete List of Published Work in My Bibliography:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1flr8NTIlsSAI/bibliography/41294769/public/?sort=date&direction=descending> (see Appendix for a manuscript accepted for publication but not published).

## D. RESEARCH SUPPORT

### Ongoing Research Support

Neural Mechanism of Fear Generalization in Children with Clinical Anxiety

Cha (PI)

Funding: Brain & Behavior Research Foundation; Type: NARSAD Young Investigator Award

Overall Goals: This NARSAD award will support my travel to Dr. Klaas Stephan's (advisor; see Biosketch-Stephan) lab at ETH Zurich in Zurich, Switzerland to learn hierarchical Bayesian modeling as a tool to study fear generalization. This award and the K01 Career Development award will work synergistically to help me become an expert in the Bayesian modeling approach to fear generalization (see 4. Career Development/Training Activities During Award Period).

Project Period: 01/15/16-01/14/18

Individual-Level Assessment of Disrupted Cortical Feedback in Affective Disorders

Cha (PI)

Funding: Columbia University and University of Glasgow; Type: Research Exchange Fellowship

Project Period: 02/01/15-01/31/17

Overall Goals: To assess cortical feedback mechanism in the visual system in patients with affective disorders. This fellowship supports the collaboration with Dr. Lars Muckli in the Institute of Neuroscience and Psychology at the University of Glasgow.

Neurodevelopmental Trajectories of Fear Generalization and the Brain Circuitry

Cha (PI)

Funding: New York State Psychiatric Institute; Type: MRI Pilot Award

Project Period: 07/16/15-07/15/16

Overall Goals: To collect pilot multimodal and fear-generalization fMRI (up to 20 hours of scan time) to optimize scanning parameters (e.g., multi- vs. single-band EPI or b values of DTI) and to estimate accurately a statistical power for a larger scale study.

**Completed Research Support**

None

**BIOGRAPHICAL SKETCH**

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

NAME: Jonathan Eric Posner, MD

ERA COMMONS USER NAME (credential, e.g., agency login): JPOSNER

POSITION TITLE: Associate Professor of Clinical Psychiatry at Columbia University

**EDUCATION/TRAINING** (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Wesleyan University	B.A.	05/1996	Molecular Biology
SUNY Brooklyn – Downstate Medical Center	M.D.	05/2001	Medicine

**A. Personal Statement**

My research focuses on the use of MRI techniques to examine neural substrates related to impulsivity and emotional processing in a range of psychiatric disorders affecting children. After completing my clinical training in child and adolescent psychiatry, I received post-doctoral research training in developmental neuroscience and MRI methods in the Division of Child and Adolescent Psychiatry at Columbia University. Following a T32 fellowship, I was awarded a NIMH funded K23 career development award and further developed my expertise in MRI analyses with a focus on developmental psychopathology. I have since been awarded additional NIMH funding to study psychostimulant effects on emotional lability in ADHD and reward circuitry in youth with anorexia nervosa.

Pediatric neuroimaging combined with developmental neuroscience is a promising way to study neural mechanisms of debilitating mental disorders in children and adolescents. In this K01 application, Dr. Jiook Cha proposes to apply this approach to childhood anxiety with an aim to investigate neurobehavioral mechanisms of pathological anxiety. He combines pediatric neuroimaging with a task assessing fear generalization using a trans-diagnostic approach. As a primary mentor, I have worked with Dr. H Blair Simpson (co-mentor) and Dr. Jiook Cha to develop the research and training plan in this application. Dr. Simpson and I have a long-standing collaboration, have written two manuscripts together, and are collaborators on two NIH funded studies. My experience and qualifications make me well-suited to be primary mentor on the present application.

- a) Cha J, Fekete T, Siciliano F, Biezonski D, Greenhill LL, Pliszka S, Blader J, Roy A, Leibenluft E, Posner J. Neural correlates of aggression in medication naive children with ADHD: Multivariate Analysis of Morphometry and Tractography, *Neuropsychopharmacology*, in press
- b) Posner J, Hellerstein DJ, Gat I, Mechling A, Klahr K, Wang Z, McGrath P, Stewart JW, Peterson B. Antidepressants normalize the default mode network in patients with dysthymia. *JAMA Psychiatry*. 2013; 70(4):373-382 PMID:23389382.
- c) Posner J, Nagel BJ, Maia TV, Mechling A, Oh M, Wang Z, Peterson BS. Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity-disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2011;50:828-837. PMCID: PMC3155780.
- d) Posner J, Russell J, Peterson BS. The circumplex model of affect: an integrative approach to affective neuroscience, cognitive development, and psychopathology. *Dev Psychopathol*. 2005;17:715-734. PMCID: PMC236715

## B. Positions and Honors

### **Positions**

- 2001-2002 Medical Intern, Long Island Jewish Medical Center  
 2002-2003 Diagnostic Radiology Resident, NewYork-Presbyterian – Weill Cornell  
 2003-2004 Research Fellow, Columbia & NY State Psychiatric Institute  
 2004-2007 Psychiatry Resident, Columbia & NY State Psychiatric Institute  
 2007-2009 Child & Adolescent Psychiatry Fellow, Oregon Health & Science University  
 2009-2010 Research Fellow, Columbia & NY State Psychiatric Institute  
 2010-present Assistant Professor, Dept. of Psychiatry, Columbia University  
 2014-present Associate Training Director for Research, Dept. of Psychiatry, Division of Child and Adolescent Psychiatry, Columbia University  
 2014-present Chair, Grand Rounds Committee, Dept. of Psychiatry, Columbia University

### **Honors**

- 2001 Alpha Omega Alpha, Medical Honors Society  
 2001 Lucy Frank Squire Award for Excellence in Radiology, SUNY Downstate  
 2005 Travel Award, 11th Annual Symposium on Emotion, University of Wisconsin  
 2006 Outreach Award, American Academy of Child and Adolescent Psychiatry  
 2006 Outstanding General Psychiatry Research Award, American Academy of Child and Adolescent Psychiatry  
 2010 NIH Pediatric Loan Repayment Program Recipient  
 2012 Campaign for America's Kids (CFAK) Award, American Academy of Child and Adolescent Psychiatry

## C. CONTRIBUTIONS TO SCIENCE

Complete List of Published Work in MyBibliography:

[http://www.ncbi.nlm.nih.gov/sites/myncbi/jonathan.posner.1/bibliography/45061202/public/?sort=dat e&direction=ascending](http://www.ncbi.nlm.nih.gov/sites/myncbi/jonathan.posner.1/bibliography/45061202/public/?sort=date&direction=ascending)

**1. Affective neuroscience in healthy adults.** During the early part of my research career, I examined competing models of emotion theory using MRI techniques in healthy individuals. In a series of studies, we isolated neurobiological correlates underlying two dimensions of emotional experience: valence (the degree to which an emotion is pleasurable) and arousal (the degree of behavioral activation association with an emotional experience). We also demonstrated the significant role that cognition has in shaping emotional experience across individuals. These studies, along with studies by other investigators, have helped advance dimensional models of emotion as a basis of MRI investigation of emotional processing.

- a) **Posner J**, Russell J, Peterson BS. The circumplex model of affect: an integrative approach to affective neuroscience, cognitive development, and psychopathology. *Dev Psychopathol*. 2005;17:715-734. PMCID: PMC2367156
- b) Gerber AJ, **Posner J**, Gorman D, Colibazzi T, Yu S, Wang Z, Kangarlu A, Zhu H, Russell J, Peterson BS. An affective circumplex model of neural systems subserving valence, arousal, and cognitive overall during appraisal of emotional faces. *Neuropsychologia*. 2008; 46:2129-2139 PMCID: PMC2486369
- c) **Posner J**, Russell J, Gerber A, Gorman D, Colibazzi T, Yu S, Wang Z, Kangarlu A, Zhu H, Peterson BS. The neurophysiological bases of emotion: an fMRI study of the affective circumplex using emotion-denoting words. *Hum Brain Mapp*. 2009;30:883-995. PMCID: PMC2644729.
- d) Colibazzi T, **Posner J**, Wang Z, Gorman D, Gerber A, Yu S, Zhu H, Kangarlu A, Duan Y, Russell J, Peterson BS. Neural systems subserving valence and arousal during the experience of induced emotions: a functional MRI study of the circumplex model of affect. *Emotion*. 2010;10:377-389. PMID: 20515226

**2. Affective neuroscience in children with externalizing disorders.** As I advanced from a post-doctoral fellow to junior faculty, I maintained my interest in neuroscience and developmental psychopathology. I

focused my work on understanding the neurobiology underlying emotional lability in children with ADHD. I conducted a series of studies that challenged the predominant model of ADHD, which suggests that in ADHD, emotional lability arises primarily from impairments in top-down control of emotional reactions. Instead, my work suggests that children with ADHD have significant abnormalities in bottom-up emotional processing within affective circuitry. We also found that psychostimulant medication may attenuate emotional lability through their effects of limbic structures.

- a) Fair D, **Posner J**, Nagel BJ, Bathula Da, Costa Dias T, Mills K, Blythe M, Giwa A, Schmitt C, Nigg J. Atypical default network connectivity in youth with ADHD. *Biol Psychiatry*. 2010;68(12):1084-1091. PMCID: PMC2997893
- b) **Posner J**, Nagel BJ, Maia TV, Mechling A, Oh M, Wang Z, Peterson BS. Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity-disorder. *J Am Acad Child Adolesc Psychiatry*. 2011;50:828-837. PMCID: PMC3155780.
- c) **Posner J**, Rauh V, Gruber A, Gat I, Wang Z, Peterson BS. Dissociable attentional and affective circuits in medication-naïve children with attention-deficit/hyperactivity disorder. *Psychiatry Res: Neuroimaging*. 2013;213(1):24-30 PMID:23664625
- d) **Posner J**, Siciliano F, Wang Z, Liu J, Sonuga-Barke E, Greenhill L. A multimodal MRI study of the hippocampus in medication-naïve children with ADHD: What connects ADHD and depression? *Psychiatry Res: Neuroimaging*, 2014; Nov 30;224(2): 112-8. PMCID: PMC4195849

**3) Network Connectivity.** In my own laboratory, we have used MRI connectivity techniques, both resting state fMRI and diffusion MRI, to examine the organization of neural circuits across a range of psychiatric disorders. We have a particular interest in examining the mechanisms by which psychotropic medications have their salutary effects. For example, we completed a resting state fMRI study in which we examined the default mode network (DMN) in chronic depression. In that study, we found that antidepressant treatment, but not placebo, had a normalizing effect on functional connectivity within the DMN, highlighting a potential mechanism by which antidepressants are effective.

- a) **Posner J**, Maia TV, Fair D, Peterson BS, Sonuga-Barke EJ, Nagel BJ. The attenuation of dysfunctional emotional processing with stimulant medication: an fMRI study of adolescents with ADHD. *Psychiatry Res: Neuroimaging*. 2011;193:151-160. Epub 2011 Jul 22. PMCID: PMC3164556.
- b) **Posner J**, Hellerstein DJ, Gat I, Mechling A, Klahr K, Wang Z, McGrath P, Stewart JW, Peterson B. Antidepressants normalize the default mode network in patients with dysthymia. *JAMA Psychiatry*. 2013; 70(4):373-382 PMID:23389382. PMCID: PMC3935731
- c) **Posner J**, Marsh R, Maia TV, Peterson BS, Gruber A, Simpson HB. Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with Obsessive-Compulsive Disorder. *Human Brain Mapping*, 2014 Jun 35(6): 2852-60. PMCID: PMC4142493
- d) Cha J, Fekete T, Siciliano F, Biezonski D, Greenhill LL, Pliszka S, Blader J, Roy A, Leibenluft E, **Posner J**. Neural correlates of aggression in medication naive children with ADHD: Multivariate Analysis of Morphometry and Tractography, *Neuropsychopharmacology*, 2015, 40: 1717-1725. PMID: 25645374

**4. Integrating neuroscience and child psychiatry.** Throughout my career, I have worked on integrating my understanding of clinical phenomenology, treatment approaches, and emerging insights from cognitive and affective neuroscience. I have conducted this work in the domains of ADHD, impulsivity, and MRI methodology.

- a) **Posner J**, Kass E, Hulvershorn L. Using Stimulants to Treat ADHD-Related Emotional Lability. *Current Psychiatry Reports*, 2014 Oct; 16(10): 478. PMCID: PMC4243526
- b) **Posner J**, Park C, Wang Z. Connecting the dots: A review of resting connectivity MRI studies in Attention-Deficit/Hyperactivity Disorder. *Neuropsychology Review*, 2014 Mar 24(1): 3-15. PMCID: PMC4119002
- c) **Posner J**, Stewart J, Rieder R. Neurobiological formulations: integrating clinical and biological psychiatry. *Academic Psychiatry*. 2007;31:479-484. PMID: 18079510

- d) Raz A, Lieber B, Soliman F, Buhle J, **Posner J**, Peterson BS, Posner MI. Ecological nuances in functional magnetic resonance imaging (fMRI): psychological stressors, posture, and hydrostatics. *Neuroimage*. 2005;25:1-7. Epub 2005 Jan 27. PMID: 15734338.

## D. RESEARCH SUPPORT

### Ongoing Research Support

R01 MH101172 (Posner, PI)	NIMH	08/2013–07/2018
<i>Imaging Stimulant Effects on Emotional Lability in Children with ADHD</i>		
This study combines a randomized clinical trial of a stimulant medication with pre- and post-treatment MRI scanning. The aim of the study is to examine stimulant-induced effects of brain structure and function and how these stimulant-induced effects alter emotional lability in children with ADHD.		
Role: Co-Investigator		
R01 MH104648 (Marsh & Simpson, co-PIs)	NIMH	09/2014 - 08/2018
<i>Control and Reward Circuits as Targets for Repetitive Thoughts and Behaviors</i>		
This study aims to use multimodal imaging to investigate how dysfunction in neural circuits underlying cognitive control and reward processing contribute to repetitive thoughts and behaviors.		
Role: Co-Investigator		
R21 MH099388 (Posner & SteinGlass, co-PIs)	NIMH	01/2014–01/2017 (NCE)
<i>Multimodal Imaging of the Mesocortical System in Anorexia Nervosa</i>		
This study aims to use longitudinal imaging to examine the neural connectivity within reward circuitry in patients with anorexia nervosa.		
Supportive Care Grant (Posner, PI)	St. Baldrick's Foundation	07/2015–06/2016
<i>Biological Substrates of Impaired Neurocognitive Functioning</i>		
The aim of this study is to identify alterations in functional and structural brain connectivity that correlate with neurocognitive decline by collecting MRI and neuropsychological test data on survivors of pediatric brain tumors across 3 academic medical centers.		
5 P50 MH090966-05 (Gingrich, PI)	NIMH	09/2010–04/2016 (NCE)
Silvio O. Conte Center for Basic and Translational Mental Health Research: Serotonergic Modulation of Brain Development: Genetic and Pharmacologic Influences on Structure, Function, and Behavior		
Evidence indicates 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. It is hypothesized that low- during early life. It is hypothesized 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: Director of Neuroimaging Core		
R01 MH036197 (Weissman, PI)	NIMH	07/1987-01/2017 (NCE)
<i>Children at High and at Low Risk for Depression</i>		
The purpose of this study is to use MRI to identify biological vulnerability for depression based on a 3-generation study of families at high and low risk for Major Depressive Disorder.		
Role: Co-Investigator		
T32 MH095502 (Rynn, PIs)	NIMH	09/1980–06/2020
<i>Translational Research Training in Child Psychiatry</i>		
Postdoctoral research training in translational research focused on developmental neuroscience and childhood psychiatric disorders.		
Role: Associate Director of Training		

### **Completed Research Support**

K23 MH091249 (Posner, PI) NIMH 06/2010–01/2016 (NCE)  
*Inhibitory Control and Emotional Processing in Pediatric ADHD*  
The purpose of this study is to examine competing neurobiological models of ADHD using functional MRI.

Investigator-Initiated Study (Posner, PI) Shire Pharmaceuticals 10/2011–10/2015  
*Examining Emotional Lability in Patients with ADHD: An fMRI Study*  
The purpose of this study is to examine the neurobiological basis of emotional lability in patients with ADHD using functional MRI.

**BIOGRAPHICAL SKETCH**

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

NAME: Simpson, Helen Blair

ERA COMMONS USER NAME (credential, e.g., agency login): SimpsonH

POSITION TITLE: Professor of Psychiatry at Columbia University Medical Center, Columbia University

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Yale College, New Haven, CT	B.S.	05/1984	Biology
The Rockefeller University, NY, NY	Ph.D.	06/1991	Neuroscience
Cornell University Medical College, NY, NY	M.D.	05/1992	Medicine

**A. Personal Statement**

My research program is dedicated to improve the outcome of patients with anxiety disorders, obsessive-compulsive disorder (OCD), and related disorders. For the patients of today, I use clinical trial methodology to test novel treatments and to examine the best ways to combine and sequence current treatments to maximize outcome. For the patients of tomorrow, I collaborate with experts in neuroimaging, genetics, and animal modeling to examine the brain mechanisms underlying anxiety, obsessions, and compulsions. My dual training (PhD in systems neuroscience studying the brain pathways underlying learned vocalizations in the bird; MD with residency training in psychiatry) allows me to bridge different disciplines and to think in an integrated way about symptoms and mechanisms. I foster this interdisciplinary approach with my collaborations and impart it to the junior faculty members, K awardees, and research fellows that I mentor. I believe that an integrated program will lead to advances in neuroscience that can transform how we conceptualize and treat mental illness. Dr. Cha's K01 application embodies this approach, but he pursues a novel research direction: combination of a fear conditioning fMRI task and multimodal MRI to investigate the neurobehavioral mechanism of maladaptive fear processing–fear generalization in youth. I have served as Dr. Cha's co-mentor on his K01 application along with Dr. Jonathan Posner (primary mentor), and we have had a productive collaboration. My experience and qualifications make me well-suited to be a co-mentor on the present application.

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

- 1984-1985 Research Assistant for Dr. Darcy Kelley, Department of Biology, Columbia University  
 1985-1992 M.D.-Ph.D. student, Cornell University Medical College and The Rockefeller University  
 1992-1993 Intern in Internal Medicine, The Presbyterian Hospital (Columbia-Presbyterian Medical Center)  
 1993-1996 Resident in Psychiatry, The New York State Psychiatric Institute and the Presbyterian Hospital (Columbia-Presbyterian Medical Center)  
 1996-1999 Postdoctoral Clinical Fellow and Assistant in Clinical Psychiatry, Columbia University  
 1999-present Research Psychiatrist, Anxiety Disorders Clinic, The New York State Psychiatric Institute  
 1999-2006 Assistant Professor of Clinical Psychiatry, Columbia University  
 2006-2010 Associate Professor of Clinical Psychiatry, Columbia University  
 2006-present Director, Anxiety Disorders Clinic, The New York State Psychiatric Institute  
 2010-2013 Professor of Clinical Psychiatry, College of Physicians and Surgeons, Columbia University  
 2013-present Professor of Psychiatry at Columbia University Medical College, Columbia University

**Honors and Awards**

1983	Phi Beta Kappa, Yale Science and Engineering Award
1984	Summa Cum Laude, Distinction in Biology, Robin Berlin Memorial Prize
1985-1992	National Research Service Award for training in The Rockefeller University-Cornell University Medical College M.D.-Ph.D. Program
1987	Alpha Omega Alpha
1992	Oscar Diethelm Prize in Psychiatry, Cornell University Medical College
1994	NIMH Outstanding Resident Award
1996	Horwitz Award for Clinical Excellence, Columbia University
1999	Junior Investigator, American Psychiatric Association's Research Colloquium
2005	NARSAD Young Investigator Award
2010	NARSAD Independent Investigator Award
2012	Elected Member of the American College of Neuropsychopharmacology
2014	The Karmason Award ("for pioneering research on the causes of and treatments for anxiety and related disorders"), Weill Cornell Medical College

**Other Experience and Professional Memberships**

2005	Appointed to the workgroup to develop OCD practice guidelines for the American Psychiatric Association (published in the American Journal of Psychiatry, 2007)
2006	Selected to be on the Scientific Advisory Board of the Anxiety Disorders Association of America
2007	Presented research to the National Advisory Mental Health Council
2008-2010	Vice-chair of the Scientific Advisory Board of the Anxiety Disorders Association of America
2009-2013	Advisor and Workgroup Member of the DSM-5 Anxiety, OC Spectrum, PTSD, and Dissociative Disorders Workgroup (Chair: Dr. Kathy Phillips) and of the Obsessive Compulsive Spectrum Disorders sub-work group (Chair: Dr. Dan Stein)
2009-2014	Standing member of the Interventions Committee for Adult Disorders (ITVA) for NIMH
2010-2012	Chair of the Scientific Advisory Board of the Anxiety Disorders Association of America
2012-2015	Member of the Working Group on the Classification of OC- and Related Disorders, WHO
2014-present	Chair of ZMH1 ERB-B (01) R (Confirmatory Efficacy Clinical Trials of Non-Pharmacological Interventions for Mental Disorders, R01) for NIMH

**C. Contribution to Science**

1. In clinical trials conducted in collaboration with Dr. Edna Foa (University of Pennsylvania), I developed evidence for how to combine and sequence first-line treatments for OCD. These data have influenced practice guidelines for treating OCD.
  - a. **Simpson HB**, Franklin ME, Cheng J, Foa EB, Liebowitz MR: Standard criteria for relapse are needed in obsessive-compulsive disorder. Depression and Anxiety 2005; 21(1): 1-8. PMCID: Policy Exempt
  - b. **Simpson HB**, Foa EB, Liebowitz MR, Ledley DR, Huppert JD, Cahill S, Vermes D, Schmidt AB, Hembree E, Franklin M, Campeas R, Hahn C-G, Petkova E: A randomized, controlled trial of cognitive-behavioral therapy for augmenting pharmacotherapy in obsessive-compulsive disorder. American Journal of Psychiatry 2008; 165(5):621-630. PMCID: PMC3945728
  - c. **Simpson HB**, Foa EB, Liebowitz MR, Huppert JD, Cahill S, Maher MJ, McLean CP, Bender J, Marcus SM, Williams MT, Waver J, Vermes D, Van Meter PE, Rodriguez CI, Powers M, Pinto A, Imms P, Hahn C, Campeas R: Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: A randomized clinical trial. JAMA Psychiatry 2013; 70(11): 1190-9. PMCID: PMC3955365
  - d. Foa EB, **Simpson HB**, Rosenfield D, Liebowitz MR, Cahill S, Huppert JD, Bender J, McLean CP, Maher MJ, Campeas R, Hahn C, Imms P, Pinto A, Powers MB, Rodriguez CI, Van Meeter PE, Vermes D, Williams MT: Six-month outcomes from a randomized trial augmenting serotonin reuptake inhibitors with exposure and ritual prevention or risperidone in adults with obsessive-compulsive disorder. Journal of Clinical Psychiatry 2015; 76(4): 440-446. NIHMSID: NIHMS695186
2. In collaboration with imaging experts, I have investigated neurochemical systems in OCD, using positron emission tomography and magnetic resonance spectroscopy. These studies challenged the serotonergic hypothesis of OCD and were the first to demonstrate cortical GABA abnormalities in OCD; I have also demonstrated abnormalities in cognitive control and reward circuits in OCD with task-based fMRI.

- a. **Simpson HB**, Lombardo I, Slifstein M, Huang HY, Hwang DR, Abi-Dargham A, Liebowitz MR, Laruelle M: Serotonin transporters in obsessive-compulsive disorder: a positron emission tomography study with [<sup>11</sup>C] McN 5652. *Biological Psychiatry* 2003; 54:1414-21. PMCID: Policy Exempt
  - b. **Simpson HB**, Slifstein M, Bender J, Xu X, Hackett E, Maher MJ, Abi-Dargham A: Serotonin 5-HT2A receptors in OCD: a PET study with [<sup>11</sup>C] MDL 100907. *Biological Psychiatry* 2011; 70(9): 897-904. PMCID: PMC3951757
  - c. **Simpson HB**, Shungu DC, Bender J, Mao X, Xu X, Slifstein M, Kegeles LS: Investigation of cortical glutamate-glutamine and γ-aminobutyric acid in obsessive-compulsive disorder by Proton Magnetic Resonance Spectroscopy. *Neuropsychopharmacology* 2012; 37(12): 2684-2692. PMCID: PMC3473334
  - d. Marsh R, Tau GZ, Wang Z, Huo Y, Liu G, Hao X, Packard MJ, Peterson BS, **Simpson HB**: Reward-based spatial learning in unmedicated adults with obsessive-compulsive disorder. *American Journal of Psychiatry* 2015; 172(4): 383-392. PMCID: PMC4382407
3. I mentor the next generation of patient-oriented translational researchers.
    - a. Wang L, **Simpson HB**, Dulawa SC: Assessing the validity of current genetic mouse models of obsessive-compulsive disorder. *Behavioural Pharmacology* 2009; 20(2): 119-133. PMCID: PMC2762389
    - b. Ahmari SE, Spellman T, Douglass NL, Kheirbek MA, **Simpson HB**, Deisseroth K, Gordon JA, Hen R: Repeated cortico-striatal stimulation generates persistent OCD-like behavior. *Science* 2013; 340(6137): 1234-9. PMCID: PMC3954809
    - c. Pinto A, Steinglass JE, Greene AL, Weber EU, **Simpson HB**: Capacity to delay reward differentiates obsessive-compulsive disorder and obsessive-compulsive personality disorder. *Biological Psychiatry* 2014; 75(8): 653-659. PMCID: PMC3969772
    - d. Rodriguez CI, Kegeles LS, Levinson A, Feng T, Marcus SM, Vermes D, Flood P, **Simpson HB**: Randomized controlled trial crossover trial of ketamine in obsessive-compulsive disorder: Proof-of-concept. *Neuropsychopharmacology* 2013; 38(12): 2475-2483. PMCID: PMC3799067 [This won the Neator Award for best paper in Neuropsychopharmacology in 2013.]
  4. I have written practice guidelines for OCD and advised on the diagnostic classification of OCD and related disorders for both the American Psychiatric Association and the World Health Organization.
    - a. Koran LM, Hanna GL, Hollander E, Nestadt G, **Simpson HB**: Practice guideline for the treatment of patients with obsessive-compulsive disorder. *American Journal of Psychiatry* 2007; 164 (7Suppl): 5-53. PMCID: Policy Exempt
    - b. Koran LM, **Simpson HB**: Guideline Watch: Practice guidelines for the treatment of patients with obsessive-compulsive disorder (*on-line publication at APA.org*). PMCID: Policy Exempt
    - c. Leckman JF, Denys D, **Simpson HB**, Mataix-Cols D, Hollander E, Saxena S, Miguel E, Rauch S, Goodman W, Phillips KA, Stein DJ: OCD: A review of the diagnostic criteria and possible subtypes and dimensional specifiers for DSM-V. *Depression and Anxiety* 2010; 27(6): 507-527. PMCID: PMC3974619
    - d. **Simpson HB**, Reddy J: Obsessive-compulsive disorder for ICD-11: Proposed changes to the diagnostic guidelines and specifiers. *Revista Brasileira de Psiquiatria* 2014; 36(Suppl 1): 3-13. PMCID: Policy Exempt

#### **Complete List of Published Work in MyBibliography:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/helen.simpson.1/bibliography/45280696/public/?sort=date&direction=ascending>

#### **D. Research Support**

##### **Ongoing Research Support**

Attaining and Maintaining Wellness in OCD

Simpson (PI)

Funding: NIMH R01 MH045436; Project Period: 7/1/12-6/30/16

Overall Goals: To examine whether those who attain wellness from combining medications and cognitive-behavioral therapy can then maintain wellness if they discontinue their medications.

Role: PI

Control and Reward Circuits as Targets for Repetitive Thoughts and Behaviors

Simpson&Marsh (PIs)

Funding: NIMH R01 MH104648; Project Period: 11/1/14-11/1/19

Overall Goals: To study cognitive control and reward circuits in OCD.

Role: PI (Co-PI: Dr. Rachel Marsh)

Improving the Control of Fear: Healthy Adults to Pathological Anxiety

Dunsmoor (PI)

Funding: NIMH K99 MH106719; Project Period: 4/15/2015-3/31/2017

Overall Goals: To improve the control of fear and to identify biobehavioral risk/resilience factors.

Role: Co-Principal Mentor (Co-Principal Mentor: Dr. Elizabeth Phelps)

Neurogenesis and Pattern Separation: A Possible Therapeutic Target for Anxiety

Klemenhagen (PI)

Funding: NIMH KL2 TR000081; Project Period: 8/15/2014-6/30/2016

Overall Goals: This project aims to create translational behavioral tests, based on neurogenesis-sensitive rodent pattern separation tasks, for use in anxiety populations.

Role: Mentor

Novel Interventions for Adults with OCD

Rodriguez (PI)

Funding: NIMH K23 MH092434; Project Period: 7/1/2011-6/30/2016

Overall Goals: This enables the PI to pursue a training and research program in novel treatments for OCD.

Role: Mentor

**Completed Research Support (last three years)**

Enhancing Patient-Oriented Research and Training in OCD

Simpson (PI)

Funding: NIMH K24 MH091555; Project Period: 2/1/10-1/31/15 (NCE to 1/31/16)

Overall Goals: This training grant will enhance patient-oriented research and training in OCD.

Role: PI

Novel Medication Strategies to Target Brain Mechanisms in Pediatric OCD

Simpson&Rynn (PIs)

Funding: NIMH Collaborative R34 MH095502; Project Period: 7/1/12-6/30/15 (NCE to 6/30/16)

Overall Goals: To study the effects of minocycline on brain glutamate and OCD severity in childhood OCD.

Role: PI (Co-PI: Dr. Moira Rynn)

Multimodal Imaging in Anorexia Nervosa

Steinglass&Posner (PIs)

Funding: NIMH R21 MH099388; Project Period: 1/13/2014-12/31/2015

Overall Goals: To study mesocortical functional and structural connectivity in Anorexia Nervosa.

Role: Co-Investigator

Distinct and Common Neural Correlates of Fear, OCD, and Eating Disorders

Simpson&Fyer&Schneier (PI)

Funding: NIMH R01 MH091694; Project Period: 7/26/11-4/30/14

Overall Goals: To examine the relationship between OCD, social phobia, and anorexia nervosa.

Role: PI (Co-PIs: Drs. Frank Schneier and Abby Fyer)

A fMRI Study of Three Neural Systems Implicated in OCD

Marsh&Simpson (PI)

Funding: R21 MH093889; Project Period: 8/1/11-7/31/13

Overall Goals: This study used fMRI imaging to examine activity in fronto-striatal control, habit learning, and reward processing circuits in OCD patients compared to healthy controls.

Role: PI (Co-PI: Dr. Rachel Marsh)

**BIOGRAPHICAL SKETCH**

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

NAME: Moira Ann Rynn, MD

ERA COMMONS USER NAME (credential, e.g., agency login): MOIRARYNN

POSITION TITLE: Ruane Professor of Psychiatry

**EDUCATION/TRAINING** (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Goucher College, Towson MD	B.A.	1985	Biology
University of Medicine and Dentistry of New Jersey New Jersey Medical School, Newark, NJ	M.D.	1991	Medicine
Hospital of the University of Pennsylvania Philadelphia, PA	Resident	1995	Psychiatry
Children's Hospital of Philadelphia Philadelphia, PA	Child & Adolescent Residency	1997	Psychiatry
Hospital of the University of Pennsylvania Philadelphia, PA	Neuropsychopharmacology Research Fellowship	1998	Psychiatry

**A. Personal Statement**

During the course of my academic career I have focused on the treatment of childhood anxiety disorders and some work in the area of pediatric depression. I have served either as principal investigator or co-principal investigator on numerous controlled pediatric clinical trials that have involved the study of medications as monotherapy or in combination with psychosocial treatments and have led seminal medication clinical trials in pediatric anxiety. I was co-PI for the NIMH funded multi-site "Child/Adolescent Anxiety Multimodal Treatment Study (CAMS)" (MH064092) and "Child/Adolescent Anxiety Multimodal Extended Long-term Study (CAMELS)" (MH064092) at our site as well as a co-investigator on the Pediatric Obsessive-Compulsive Disorder (OCD) Treatment Study (MH55126). More recently, my area of research has expanded to working with children and adolescents with anxiety disorders who have failed first line treatments, and to examining the potential underlying mechanism of pediatric anxiety disorders.

In this proposal, Dr. Cha proposes translational neuroimaging research in anxious youth with sophisticated, interdisciplinary methodology and dimensional sampling across the spectrum of anxiety. I will continue to advise Dr. Cha on his research proposal and career development training activities in phenomenology, and characterization of pediatric anxiety disorders. My experience and qualifications make me well-suited to be an advisor on this application.

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

1994-95	Chief Resident in Psychiatry, Hospital of the University of Pennsylvania, Philadelphia, PA
1995-97	Fellowship, Child and Adolescent Psychiatry, Children's Hospital of Philadelphia, Child Guidance Center, University of Pennsylvania School of Medicine, Philadelphia, PA
1996	American Board of Psychiatry and Neurology Certification in Adult Psychiatry
1997	Child and Adolescent Psychiatry Fellowship and Board Certified

1997-98	Neuropsychopharmacology Training Program, UPENN, Department of Psychiatry
1998-06	Assistant Professor, Department of Psychiatry, UPENN
1998-06	Medical Director of the Mood and Anxiety Disorders Section, Department of Psychiatry, UPENN
2006-2014	Associate Professor of Clinical Psychiatry, Department of Psychiatry, Division of Child and Adolescent Psychiatry, New York State Psychiatric Institute, Columbia University
2006-2012	Deputy Director, Child and Adolescent Psychiatry Research, New York State Psychiatric Institute
2012-2014	Interim Director of the Child and Adolescent Psychiatry Division, New York State Psychiatric Institute, Columbia University
2014-present	Director of the Child and Adolescent Psychiatry Division, New York State Psychiatric Institute, Columbia University
2014-present	Ruane Professor of Psychiatry, Department of Psychiatry, Division of Child and Adolescent Psychiatry, New York State Psychiatric Institute, Columbia University

### **Honors**

1990	Ivan Gorkun Annual Scholarship for Leadership and Academic Excellence of the New Jersey Medical School Alumni Association
1995	Dr. Henry P. & M. Page Durkee Laughlin Foundation Merit Award
1996	American Medical Association /Glaxo Wellcome Achievement Award
1998	University of Pennsylvania, Department of Psychiatry, 3rd and 4th year Resident Teaching Award
2005	Martin P. Szuba Award for Excellence in Clinical Teaching and Research, Department of Psychiatry, University of Pennsylvania School of Medicine
2006	The Earl Bond Award, Department of Psychiatry, University of Pennsylvania
2010	Best Doctors in America ® (2006, 2008, 2009, 2011)

### **Other Experience and Professional Memberships**

1997-2006	Regional Council of Child and Adolescent Psychiatry, Pennsylvania
1997-present	American Academy of Child and Adolescent Psychiatry
2005-2008	American Foundation for Suicide Prevention Scientific Advisory Council
2008-Present	Member of the Mental Health Services Council appointed by the Governor, New York State Office of Mental Health
2008-Present	Member of the Work Group on Research, American Academy of Child and Adolescent Psychiatry

### **C. Contribution to Science**

**1. GENERALIZED ANXIETY DISORDER** –I have conducted and participated in multiple single site and multi-site clinical trials of medications for the treatment of anxiety disorders that have produced results which have significantly contributed to treatment for pediatric anxiety disorders. I have also led seminal clinical trials in pediatric anxiety including the study of sertraline and venlafaxine extended release for pediatric generalized anxiety disorder. I was co-principal site investigator for the multi-site “Child/Adolescent Anxiety Multimodal Treatment Study” (U01 MH64092-07), a clinical trial comparing medication and CBT for children with anxiety disorders. I am currently collaborating on a clinical and translational research pilot program, which is measuring mechanism of action for potential new treatment approaches and correlating findings to diagnosis and treatment response in children with anxiety disorders.

- a. Rynn MA, Riddle MA, Yeung PP, Kunz NR: Efficacy and Safety of Extended-Release Venlafaxine in the Treatment of Generalized Anxiety Disorder in Children and Adolescents: Two Placebo-Controlled Trials. *American Journal of Psychiatry* 2007; 164(2):290–300.
- b. Rynn M, Russell J, Erickson J, Detke MJ, Ball S, Dinkel J, Rickels K, Raskin J: Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depression and Anxiety* 2008;25(3):182–189.
- c. Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, Ginsburg GS, Rynn MA, McCracken J, Waslick B, Iyengar S, March JS, Kendall PC: Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *New England Journal of Medicine* 2008; 359(26):2753–2766.

- d. Rynn M, Walkup JT, Compton SN, Sakolsky DJ, Sherrill JT, Shen S, Kendall PC, McCracken J, Albano AM, Piacentini J, Riddle MA, Keeton C, Waslick B, Chrisman A, Iyengar S, March JS, Birmaher B. Child/Adolescent anxiety multimodal study: Evaluating safety. *Journal of the American Academy of Child and Adolescent Psychiatry*, 2015; 54:180–190.

**2. OBSESSIVE-COMPULSIVE DISORDER** – For the past several years I have been studying novel medication strategies to treat Obsessive-Compulsive Disorder in pediatric patients who do not respond to first line treatments. I was a co-investigator on the Pediatric OCD Treatment Study (R01MH55126) and, most recently, am studying novel compounds for treatment of pediatric OCD targeting brain mechanisms utilizing MRS techniques (R34MH095502-02). I am also the co-principal investigator (co-pi) on a study of *Novel OCD medication strategies to target brain mechanisms in adolescents*, a NIMH-funded clinical trial paired with MRS to examine the feasibility, efficacy, and mechanism of antibiotic augmenting of SSRIs for children and adolescent diagnosed with OCD (R43MH095502). I am also currently co-pi investigator on a foundation funded study evaluating the feasibility/tolerability, and preliminary efficacy of ketamine, a medication that modulates glutamate in the brain, as a rapid treatment for OCD symptoms in adolescents with OCD. I am co-pi on the study, *Overlapping Neural Circuits Implicated in Obsessive-Compulsive Disorder* in which Functional MRI is being used to understand how dysfunction in overlapping fronto-striatal neural circuits contributes to OCD by impairing control over intrusive thoughts (obsessions) and repetitive behaviors (compulsions) and diminishing the capacity to process rewards in children.

- a. The Pediatric OCD Treatment Study (POTS) Team: Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA* 2004; 292(16):1969–1976.
- b. Rodriguez CI, Bender J, Glazier K, Rynn M, Simpson HB: An open-Label trial of minocycline, a glutamate modulator, in treatment-resistant adults with the obsessive compulsive disorder. 49th annual NCDEU, 2009.
- c. Rodriguez C, Bender J, Marcus S, Snape M, Rynn M, Simpson H: Minocycline augmentation of pharmacotherapy in obsessive-compulsive disorder: an open-label trial. *Journal of Clinical Psychiatry* 2010; 71(9):1247–1249

### **3. DEPRESSION AND BIPOLAR DISORDERS**

I served as co-investigator and co-pi on clinical trials that have assessed treatment efficacy of medication and psychotherapy for pediatric major depression and bipolar disorder. I am co-pi of a study entitled “*A Stepped Care Model of Adolescent Depression Treatment in Primary Care*” in which we are assessing the preliminary acceptability, feasibility, and effectiveness of a novel collaborative stepped care model of treatment for depressed Latino adolescents in the pediatric primary care setting (5R34MH091320-03).

- a. Rynn M, Wagner KD, Donnelly C, Ambrosini P, Wohlberg CJ, Landau P, Yang R: Long-term sertraline treatment of children and adolescents with major depressive disorder (MDD). *Journal of Child and Adolescent Psychopharmacology* 2006; 16(1–2):103–116.
- b. Biernacki C, Martin P, Goldberg PH, Rynn MA (in press). Treatments for Pediatric Depression. In P.E. Nathan & J.M. Gorman (Eds.), *A Guide to Treatments That Work* (4th ed.). New York: Oxford University Press.
- c. Goldberg PH, Martin P, Biernacki C, Rynn MA (in press). Treatments for Pediatric Bipolar Disorder. In P.E. Nathan & J.M. Gorman (Eds.), *A Guide to Treatments That Work* (4th ed.). New York: Oxford University Press
- d. Findling RL, Robb, A, McNamara NK, Pavuluri MN, Kafantaris V, Scheffer R, Frazier JA, Rynn M, DelBello M, Kowatch RA, Rowles BM, Lingler J, Martz K, Anand R, Clemons TE, Taylor-Zapata P: Lithium in the acute treatment of a manic or mixed episode in pediatric bipolar disorder: a randomized, double-blind, placebo-controlled study. *Pediatrics* 2015, in press.

**4. TRAINING NEXT GENERATION OF CLINICIAN-RESEARCHERS** – I play a significant role as mentor of trainees and junior faculty who will comprise the next generation of child and adolescent psychiatrists and clinician-researchers. There are not sufficient numbers of child and adolescents psychiatrists nationwide pursuing research. As co-principal investigator of the NIMH-funded Translational Research Training in Child Psychiatry (2 T32 MH016434-36), and chair the Executive Committee (EC) comprised of faculty members

whose expertise is neuroscience, clinical, or epidemiological research, I help oversee the process for trainee selection and meet regularly with fellows throughout their training, to assist their progress and help guide career planning. I oversee the financial administration and the coordination of this prestigious fellowship with other research and clinical fellowships at Columbia. Additionally, I am responsible for ensuring that research fellows receive priority in accessing the many institutional core resources that are available to trainees and faculty members.

- **Complete List of Published Work in My Bibliography:**  
<http://www.ncbi.nlm.nih.gov/pubmed?term=moira+rynn>

## D. Research Support

### Ongoing Research Support

NIMH, 2 T32 MH016434-36	Marsh (Co-PI)/Rynn (Co-PI)	07/01/2015-06/30/2020
Translational Research Training in Child Psychiatry		
This training program will produce translational scientists who study the causal pathways underlying psychiatric symptoms and improve the treatment of neurodevelopmental illnesses. Our integrated training program will launch neuroscience-oriented clinician-scientists and translationally-oriented basic neuroscientists, all of whom will carry a cross-disciplinary perspective forward into their independent careers.		
1R34MH095502-01A1	Rynn (Co-PI) / Simpson (Co-PI)	06/2012-05/2016 (NCE)
This study will examine the feasibility, clinical efficacy, and potential mechanism of a novel medication treatment strategy: the addition of minocycline to serotonin reuptake inhibitors. If effective, minocycline could greatly improve the outcome of children and adolescents with OCD because it is cost effective and widely available in generic formulation. Additionally, the study will use state-of-the art MRS methods to determine whether the addition of minocycline leads to measurable changes in striatal Glu levels and whether changes in striatal Glu levels are associated with response to minocycline.		
1R21MH101441-01A1	Marsh (Co-PI) / Rynn (Co-PI)	06/1/2014-4/31/2016
The Functioning of Overlapping Frontostriatal Circuits in Children with OCD In this project we are assessing the functioning of the neural circuits that support cognitive control, habit learning, and reward processing in un-medicated children (ages 6-12) with Obsessive-Compulsive Disorder.		
Rynn (Co-PI) / Simpson (Co-PI) 02/13/2015-01/25/2016		
Ketamine Treatment for Pediatric-Refractory Obsessive Compulsive Disorder (OCD) This pilot study will determine the acceptability, feasibility and potential efficacy of ketamine as a rapid treatment for obsessive-compulsive disorder (OCD) symptoms in adolescents and young adults with OCD. Promising data will lead to a grant application to the National Institutes of Mental Health for a full-scale randomized controlled trial.		
1R34MH091320-01A1	Rynn (Co-PI) / Mufson (Co-PI)	09/2011-8/2015 (NCE)
The overall aim of this study is to assess the feasibility and acceptability of a stepped model of collaborative care (SCiPT-A) for adolescent depression delivered by social workers in pediatric clinics serving minority adolescents who face significant challenges in accessing mental health care.		

### Completed Research Support (in the last three years)

2R01MH064092-07A1	Albano (PI)/Rynn (Co-PI)	1/2010-03/30/2015 (NCE)
1/6 Child/Adolescent Anxiety Multimodal Extended Long-term Study (CAMELS) The goal of this study is to follow up a sample of children and adolescents (N=488) with anxiety disorders that participated in the multi-site collaboration of the Child/Adolescent Anxiety Multi-modal Study (CAMS), to examine the long-term psychiatric, physical, and functional outcomes of youth with anxiety disorders who were randomized to one of four treatment conditions (i.e., cognitive behavioral therapy (CBT), sertraline (SRT), pill placebo, or combined CBT + SRT).		

Lilly USA, LLC

Rynn (PI)

6/2011-12/2013

A Double-Blind, Efficacy and Safety Study of Duloxetine versus Placebo in the Treatment of Children and Adolescents with Generalized Anxiety Disorder – Protocol F1-MC-HMGI  
The primary objective of this study is to assess whether duloxetine is superior to placebo in the acute treatment of children and adolescents diagnosed with Generalized Anxiety Disorder. The goal is also to examine the efficacy, safety and tolerability of duloxetine in the treatment of pediatric Generalized Anxiety Disorder.

**BIOGRAPHICAL SKETCH**

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

NAME: Daniel S. Pine

ERA COMMONS USER NAME (credential, e.g., agency login): Pineds

POSITION TITLE: Tenured Investigator; Branch Chief; Section Chief

**EDUCATION/TRAINING** (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Grinnell College, Grinnell, Iowa	BS	06/1985	Anthropology
University of Chicago, Chicago, Illinois	MD	06/1990	Medicine
Columbia University, New York, New York	Resident	06/1994	Psychiatry
Columbia University, New York, New York	Fellow	06/1996	Child Psychiatry

**A. Personal Statement**

I currently direct a research program at the National Institute of Mental Health Intramural Research Program (NIMH-IRP) focused on the neuroscience of normal and abnormal fear, including related symptoms of anxiety. My particular focus is on using insights from neuroscience to inform understandings of risk, diagnosis, and treatment of anxiety disorders. This research focus—translational neuroscience research in pediatric anxiety—makes me ideal for the role as an advisor in this K01 application. My experience and qualifications make me well-suited for this role.

I will provide hands-on training in psychobiological and functional neuroimaging experimentation using fear conditioning paradigms at NIMH. I will also meet once every two months to discuss the progress of research and training and how to link knowledge from neuroscience to psychopathology of anxiety disorders to improve diagnosis and treatment.

**B. Positions and Honors**

- 1993-1997 Clinical Director, Neurobiological Core of the Lowenstein Center, Columbia University
- 1996-1998 Associate Director, Psychophysiological/Biological Core of the Center for the Study of Youth Anxiety, Depression, and Suicide (MHCRC-10456), Columbia Univ./NY State Psychiatric Institute (CU/NYSPI)
- 1996-1998 Assistant Professor of Clinical Psychiatry, Division of Child Psychiatry, CU/NYSPI
- 1998-2000 Associate Professor of Clinical Psychiatry; Division of Child Psychiatry, CU/NYSPI
- 1998-2000 Director of Developmental Biological Research; Division of Child Psychiatry, CU/NYSPI
- 1999-2000 Director, Clinical Core of the Intervention Research Center, Division of Child Psychiatry, CU/NYSPI

- 2000-Present Chief, Section on Development and Affective Neuroscience (SDAN) with Tenure; Chief, Child and Adolescent Research; Mood and Anxiety Program, Intramural Research Program, NIMH
- 2006-Present Chief, Emotion and Development Branch, Mood and Anxiety Program, Intramural Research Program, NIMH

### Honors, Awards, & Committee Membership

Phi Beta Kappa, Mortar Board - Grinnell College  
Robinson-Cunningham Award, American Academy of Child and Adolescent Psychiatry  
Blanche Ittelson Award, American Psychiatric Association  
Joel Elkes Award, American College of Neuropsychopharmacology  
Fellow, American Psychiatric Association  
Ruane Award for Child and Adolescent Psychiatric Research  
Institute of Medicine of National Academy of Science, Member  
DSM-5 Task Force on Anxiety Disorders

### C. Contribution to Science

One contribution heavily informs my current research focus, on defining the neural correlates of pediatric anxiety disorders. This work has used a range of neuroscience techniques, including neuro-morphometry, resting-state functional magnetic resonance imaging (fMRI), and electrophysiology. However, my most consistent approach relies on task-based fMRI to define the neural correlates of various anxiety states, particularly generalized anxiety disorder and social anxiety disorder. This work uses multiple tasks to interrogate four sets of psychological processes and associated circuitry: 1) bottom-up capture of attention, 2) threat appraisal, 3) fear learning, including conditioning and extinction, as well as 4) aspects of executive functions, including cognitive control, decision making, and reward processing. This work has generated more than 100 peer-reviewed publications. Representative examples appear below.

1. McClure EB, Monk CS, Nelson EE, Parrish JM, Adler A, Blair RJR, Fromm S, Charney DS, Leibenluft E, Ernst M, **Pine DS**: Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. *Arch Gen Psychiatry* 2007; 64: 97-106.
2. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, Chen G, McClure-Tone EB, Ernst M, **Pine DS**: Amygdala and prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Arch Gen Psychiatry* 2008; 65: 568-76.
3. Guyer AE, Choate VR, Detloff A, Benson B, Nelson EE, Perez-Edgar K, Fox NA, **Pine DS**, Ernst M: Striatal functional alterations during incentive anticipation in pediatric anxiety disorders. *Am J Psychiatry* 2012; 169: 205-12.
4. Britton JC, Grillon C, Lissek S, Norcross MA, Szuhany KL, Chen G, Ernst M, Nelson EE, Leibenluft E, Sheehner T, **Pine DS**: Response to learned threat: an fMRI study in adolescent and adult anxiety. *Am J Psychiatry* 2013; 170: 1195-1204.

A second contribution defines the shared and condition-specific neural correlates of pediatric anxiety disorders and behavioral inhibition, a temperament manifested in children's first years of life and predictive of later risk for anxiety disorders. This work uses a common set of techniques to study behavioral inhibition and pediatric anxiety disorders, to compare and contrasts the correlates of anxiety and inhibition. Particularly notable findings link perturbed bottom-up capture of attention and cognitive control in both anxiety and behavioral inhibition. Representative examples from the published literature appear below.

1. Hardee JE, Benson BE, Bar-Haim Y, Mogg K, Bradley BP, Chen G, Britton JC, Ernst M, Fox NA, **Pine DS**, Perez-Edgar K: Patterns of neural connectivity during an attention bias task moderate associations between early childhood temperament and internalizing symptoms in young adulthood. *Biol Psychiatry* 2013; 74: 273-79.

2. Guyer AE, Benson B, Choate VR, Bar-Haim Y, Perez-Edgar K, Jarcho JM, **Pine DS**, Ernst M, Fox NA, Nelson EE: Lasting associations between early-childhood temperament and late-adolescent reward-circuitry response to peer feedback. *Dev Psychopathol* 2014; 26: 229-243.
3. Jarcho J, Fox NA, **Pine DS**, Leibenluft E, Shechner T, Degnan KA, Perez-Edgar K, Ernst M: Enduring influence of early temperament on neural mechanisms mediating attention-emotion conflict in adults. *Depress Anx* 2014; 31; 53-62.
4. Lahat A, Lamm C, Chronis-Tuscano A, **Pine DS**, Henderson HA, Fox NA: Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *J Am Acad Child Adolesc Psychiatry* 2014; 53; 447-455.

My third contribution examines therapeutics. While I have studied various psychiatric conditions, my research most deeply involves anxiety disorders. I conducted some of the first studies on the safety and efficacy of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents. This work led to basic science research on SSRIs and service on Food and Drug Administration committees. I continue to examine SSRI effects. Another particularly deep focus uses research in neuroscience to generate novel treatments. Again, my work on anxiety has been most extensive, where I am currently examining the efficacy and neural effects of attention bias modification treatment (ABMT). Representative examples from the published literature appear below.

1. The RUPP Anxiety Study Group (**DS Pine**, corresponding author): Fluvoxamine for anxiety disorders in children and adolescents. *N Engl J Med* 2001; 344: 1279-1285.
2. Brotman LM, Gouley KK, Chesir-Teran D, Kamboukos D, Huang K-Y, Fratto C, **Pine DS**: Effects of a psychosocial family-based preventative intervention on cortisol response to a social challenge in preschoolers at high risk for psychopathology. *Arch Gen Psychiatry* 2007; 64: 1172-9.
3. Hakamata Y, Lissek S, Bar-Haim Y, Britton JC, Fox NA, Leibenluft E, Ernst M, **Pine DS**: Attention bias modification treatment: a meta-analysis towards the establishment of novel treatment for anxiety. *Biol Psychiatry* 2010; 68: 982-90.
4. Eldar S, Apter A, Lotan D, Perez-Edgar K, Naim R, Fox NA, **Pine DS**, Bar-Haim Y: Attention bias modification treatment for pediatric anxiety disorders: a randomized controlled trial. *Am J Psychiatry* 2012; 169; 213-20.

A fourth contribution charts outcome of pediatric mental disorders. As with my research on neuroscience and therapeutics, this work focuses on emotional conditions, particularly anxiety. Thus, more than 20 years ago, I showed that pediatric anxiety disorders carried a high risk for both adult mood and anxiety disorders, research that has been widely replicated. I also extended this work through collaborations with Dr. Nathan Fox to demonstrate strong longitudinal associations among behavioral inhibition during early childhood, anxiety disorders during adolescence, and mood disorders in adulthood. Other aspects of my research on outcome focus on pediatric behavior and mood disorders. Representative publications appear below.

1. **Pine DS**, Cohen P., Gurley D., Brook J., Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders *Arch Gen Psychiatry* 1998; 55: 56-66.
2. **Pine DS**, Cohen P, Brook J: Moodiness or mood disorder? Depressive symptoms in adolescence as predictors of adult depression. *Am J Psychiatry* 1999; 156:133-135.
3. **Pine DS**, Cohen P, Brook J: Adolescent fears and risk for major depression. *Biol Psychiatry* 2001; 50:721-4.
4. Chronis-Tuscano A, Degnan KA, **Pine DS**, Perez-Edgar K, Henderson HA, Diaz Y, Raggi VL, Fox NA: Stable, early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *J Am Acad Child Adolesc Psychiatry* 2009; 48: 928-35.

A fifth contribution focuses on comorbidity among mental disorders and between mental and physical disorders. This work has addressed two main themes. First, I have used longitudinal, family-based, and neuroscience techniques to define the shared and condition-specific correlates of pediatric mental disorders. This work most deeply has contrasted pediatric anxiety disorders with pediatric mood and behavior disorders. Second, I have used longitudinal and physiological techniques to define the shared correlates of pediatric mental and physical disorders. This work has focused on emotional disorders and their relationship to dysfunction in the respiratory and cardiovascular systems. Representative publications appear below.

1. **Pine DS**, Klein RG, Coplan JD, Martinez J, Kovalanko P, Moreau D, Klein DF, Gorman JM: Differential sensitivity to CO<sub>2</sub> in childhood anxiety disorders. *Arch Gen Psychiatry* 2000; 57: 960-67.
2. Johnson J, Cohen P, **Pine DS**, Klein DF, Kassen S, Brook J: The association between cigarette smoking and anxiety disorders during adolescence and early adulthood. *JAMA* 2001; 284:2348-51
3. **Pine DS**, Wolk S, Goldstein RB, Weissman MM: The association between childhood depression and adulthood body mass index. *Pediatrics* 2001; 107: 1049-1056.
4. Blair RJR, Leibenluft E, **Pine DS**: Conduct disorder and callous unemotional traits in youth. *N Engl J Med* 2014; 371: 2207-16.

- **Complete List of Published Work in My Bibliography:**

[http://www.ncbi.nlm.nih.gov/pubmed?term=\(pine+ds%5Bauthor%5D\)](http://www.ncbi.nlm.nih.gov/pubmed?term=(pine+ds%5Bauthor%5D))

#### **D. Research Support**

Branch Chief, NIMH Intramural Research Program (2006-present);  
Section Chief, NIMH Intramural Research Program (2000-present)

**BIOGRAPHICAL SKETCH**

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

NAME: Bowman, F. DuBois

ERA COMMONS USER NAME (credential, e.g., agency login): DBOWMAN

POSITION TITLE: Professor and Chair of Biostatistics

**EDUCATION/TRAINING** (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Moregouse College, Atlanta ,GA	B.S	05/1992	Mathematics
University of Michigan, Ann Arbor, MI	M.S.	05/1995	Biostatistics
University of North Carolina, Chapel Hill, NC	Ph.D.	05/2000	Biostatistics

**A. Personal Statement**

The general objectives of this application are to prepare the PI to become an independent researcher and to conduct original research specifically to investigate fear generalization and its age-related changes in typically developing youth, associations of these changes with maturation of the corticolimbic system, and assessment of these developmental changes in pathological anxiety.

I bring over 15 years of experience in the development and application of neuroimaging statistical methods that will directly benefit this project. As a part of my research program at Columbia University (and previously at Emory University, where I founded and served as the Director of the Center for Biomedical Imaging Statistics), I have developed neuroimaging statistical methods that have focused on identifying subgroup differences in task-related alterations in brain activity, determining resting-state and task-related functional connectivity, combining both structural and functional brain imaging data to determine connectivity, and predicting clinical or behavioral outcomes from multimodal imaging, clinical, and genomics data. My neuroimaging analytic methods have targeted a range of neurological and psychiatric disorders such as major depressive disorder (MDD), Parkinson's disease, stroke, social anxiety disorder, and schizophrenia. My work also spans multiple imaging modalities including magnetic resonance imaging (MRI), functional MRI, diffusion tensor imaging (DTI), and positron emission tomography (PET).

Dr. Cha's K01 application aligns well with my research focus. I find that his proposal of multi-modal MRI and fear generalization to study the fear regulatory circuit and behavior in youths is a very important study for the progress of early detection of brain abnormalities related to anxiety disorders. As an advisor on this application, I will supervise the training on and the implementation of advanced neuroimaging statistical and computational methods in this application. My experience and qualifications as describe below make me well-suited for this role.

**B. Positions and Honors****Professional Experience:**

- 7/00-10/06 Assistant Professor, Department of Biostatistics, Emory University
- 4/01-5/01 Visiting Scholar, Department of Statistics, Carnegie Mellon University
- 8/05-10/05 Visiting Assistant Professor, Department of Biostatistics, Johns Hopkins University
- 10/06-10/13 Associate Professor (tenured), Department of Biostatistics and Bioinformatics, Emory University
- 09/07-12/13 Director, Center for Biomedical Imaging Statistics, Emory University
- 2008-2013 Neuroscience Program Faculty Member, Graduate Division of Biological and Biomedical Sciences, Emory University.

10/13-12/13 Professor (tenured), Department of Biostatistics and Bioinformatics, Emory University  
01/14-Present Chairman and Professor, Department of Biostatistics, Columbia University, Mailman School of Public Health

### **Professional Memberships and Committees:**

- 2000-present Member of American Statistical Association  
2000-present Member of International Biometric Society  
2001-present ENAR Diversity Committee (founding member)  
2003-2005 ENAR Regional Advisory Board (**RAB**), 2003-2005, appointed by President Dr. Tim Gregoire.  
2003-2012 NIH, Grant Reviewer, Biostatistical Methods and Research Design (BMRD) Study Section (2006, 2008, 2009, 2012); special emphasis panels for National Institute of Biomedical Imaging and Bioengineering (NIBIB) (2003), National Institute of Mental Health (NIMH) (2007), health services, clinical, and population health research (2009), National Institute for Child Health and Human Development (NICHD) (2012).  
2004-present Member of the Organization for Human Brain Mapping  
2004-2015 ENAR Workshop for Junior Researchers Organizing Committee/Panelist/Speaker  
2006 NIH, Reward Neurocircuitry in Adolescent Development and Decision Making Workshop, Sponsored by NIDA, NIMH, NICHD, NINDS, Invited workshop participant, Bethesda, MD, 2006.  
2007-2009 ENAR Regional Committee (**RECOM**) Member, 2007-2009, elected position.  
2014 President, ENAR of the International Biometric Society 2014; Past-Pres.-2015; Pres.-elect 2013.

### **Editorial Boards**

- Associate Editor, *Journal of American Statistical Association*, 2007-2012  
Associate Editor, *Biometrics*, 2007-2009

### **Honors and Awards:**

- 1991 Phi Beta Kappa, Golden Key Honors Society, and Pi Mu Epsilon Honorary Mathematics Society  
1992 Beta Kappa Chi Science Honors Society  
1992-1997 National Ford Foundation Predoctoral Fellow  
1993-1995 Rackham Merit Fellow, University of Michigan  
1995-2000 National Heart, Lung, and Blood Institute Trainee, University of North Carolina  
1996-1997 Minority Presence Fellow, University of North Carolina  
1997 National Ford Foundation, Honorable Mention Dissertation Fellow  
2007 Woodruff Leadership Academy 2007 Fellow, Woodruff Health Sciences Center, Emory Univ.  
2008 James E. Grizzle Distinguished Alumnus Award, 2008, Department of Biostatistics, University of North Carolina at Chapel Hill  
2012 Fellow of the American Statistical Association

### **C. Contribution to Science**

In what follows, I describe significant contributions in the development of new statistical methods to advance various scientific application areas. My developments typically target a disease area, such as Parkinson's disease or depression, and data type (e.g. imaging). I played a leading role in nearly all of the contributions discussed below, as either lead author (\*), postdoctoral or doctoral student advisor to lead author (\*), or equal scientific contributor (†).

#### **Spatio-temporal Statistical Models for Neuroimaging Data**

Functional neuroimaging data are massive and include measurements of brain activity over hundreds of time points (every two to three seconds) captured at hundreds of thousands of spatial (brain) locations. The data, therefore, contain temporal correlations as well as spatial correlations between brain locations, which manifest in complex patterns given the underlying neurophysiology that enables distant locations to exhibit high correlations. Historically, estimation methods essentially fit separate statistical models at each brain location. My research has led to vast improvements by producing rigorous frameworks for estimation and hypothesis testing, which account for spatio-temporal correlations in the data. Specifically, we developed methods that leverage neuroanatomic brain parcellations to capture the most salient short and long range correlations using hierarchical models. Our models yield the following benefits: increased precision in estimates, increased

statistical power, unified framework for activation and functional connectivity, unified framework for voxel- and region-level analyses, and generally improved modeling assumptions that are better suited to the data.

1. \*Bowman, F. D. (2007). Spatio-Temporal Models for Region of Interest Analyses of Functional Neuroimaging Data. *Journal of the American Statistical Association* 102(478): 442-453.
2. \*Bowman, F.D., Caffo, B.A, Bassett, S. and Kilts, C. (2008). A Bayesian Hierarchical Framework for Spatial Modeling of fMRI Data. *NeuroImage*, 39, 146–156 PMCID: PMC2134321.
3. \*Derado, G., Bowman, F.D. and Kilts, C. (2010). Modeling the spatial and temporal dependence in fMRI data. *Biometrics*, 66, 949-957. PMCID: PMC2942991.
4. \*Zhang, L., Agravat, S., Derado, G., Chen, S., and Bowman, F. D. (2012). BSMac: A MATLAB toolbox Implementing a Bayesian Spatial Model for Brain Activation and Connectivity. *Journal of Neuroscience Methods*, 204:133-143. PMCID:PMC3341733.

### New Methods for Determining Brain Connectivity

Connectivity studies yield important information about normal brain function and psychiatric or neurological disorders. Connectivity may refer to functional associations in neural activity between distinct brain regions (functional connectivity), influence of one region on another (effective connectivity), or anatomic links between different regions (structural). My research has made fundamental contributions, particularly in functional connectivity. We have developed model-based statistical methods for determining functional connectivity, which can be applied to both resting-state and task-based studies, while many existing methods are inherently suited for resting-state studies. One of our approaches moves beyond functional connectivity to determine hierarchical relationships between functionally connected regions, which we call ascendancy, to account for the respective roles of the connected nodes (e.g. satellite or driver) (Patel et al., 2006). This approach was shown by others to work well in a comprehensive comparison of alternative techniques (Smith et al., 2011). Recently, we have focused on multimodal approaches to determine functional connectivity (next subsection). Specifically, we developed methods that leverage aspects of structural connectivity to inform our determination of functional connectivity. One approach extends the previously developed Patel method (Xue, 2015). My research also considers whole-brain topological properties of networks, which are able to identify global properties of brain networks.

1. \*Bowman, F. D., Zhang, L., Derado, G., and Chen, S. (2012). Determining Functional Connectivity using fMRI Data with Diffusion-Based Anatomical Weighting. *NeuroImage*, 62, 1769-1779. PMCID:PMC3408852.
2. \*Patel, R., Bowman, F. D., and Rilling, J. K. (2006). A Bayesian Approach to Determining Connectivity of the Human Brain. *Human Brain Mapping* 27: 267-276. PMID:16092131.
3. Simpson, S., Bowman, F. D., and Laurienti, P. (2013). Analyzing Complex Functional Brain Networks: Fusing Statistics and Network Science to Understand the Brain. *Statistics Surveys*, 7: 1-36. PMCID:PMC4189131
4. \*Xue, W., Kang, J., Bowman, F.D., Wager, T.D., and Guo, J. (2014). Identifying Functional Co-activation Patterns in Neuroimaging Studies via Poisson Graphical Models. *Biometrics*, 70, 812–822. PMCID:PMC4276452/ PMID:25147001.

### Multimodal Statistical Models

A growing number of studies acquire data from multiple imaging modalities, reflecting distinct characteristics of brain function and structure. These data present opportunities for joint modeling and analysis. Substantial challenges arise for such modeling efforts, and only a limited number of investigators have made progress in this area. We have ongoing research in this area, with some early success in using multimodal data to determine functional connectivity. Our frameworks use structural connectivity to help inform functional connectivity. Our methods have proven to be beneficial for dissociating brain regions into groups with high within-group and low between-group correlations, particularly when groups are not clearly separable based on the functional data alone; for increasing reproducibility of results; and for increasing interpretability by revealing the extent of structural connectivity within particular functional brain networks. We also have ongoing research that integrates multimodal imaging data for prediction.

1. \*Bowman, F. D. (2014). Imaging Analysis. Annual Review of Statistics and Its Application, vol. 1: 61-85. PMCID:PMC4189192 (<http://arjournals.annualreviews.org/eprint/>)
2. \*Bowman, F. D., Zhang, L., Derado, G., and Chen, S. (2012). Determining Functional Connectivity using fMRI Data with Diffusion-Based Anatomical Weighting. *NeuroImage*, 62, 1769-1779. PMCID:PMC3408852.

3. \*Xue, W., Bowman, F.D., Pileggi, A.V., and Mayer, A.R. (2015). A Multimodal Approach for Determining Brain Networks by Jointly Modeling Functional and Structural Connectivity. *Frontiers in Computational Neuroscience*, vol. 9, article 22, 1-11.

### Prediction

The clinical impact of imaging data relies, in part, on the ability to link the data to diagnostic or prognostic clinical endpoints. My predictive modeling research has made significant contributions in this area. We developed two frameworks that use baseline imaging data and clinical information to forecast distributed maps of future brain activity (Guo et al., 2008; Derado et al., 2013). We applied our methods to predict the brain response to treatment for schizophrenia and to predict maps revealing the progression of Alzheimer's disease. We also developed statistical methods that utilize high-dimensional imaging data to predict a clinical endpoint. One limitation of current machine-learning methods is that there is no structured way to incorporate longitudinal data, and the naïve approach simply aggregates the longitudinal imaging data as independent predictors. Our work extends support vector classifiers by combining longitudinal imaging data via a linear combination with weights determined empirically from the data.

1. †Guo, Y., Bowman, F.D. & Kilts, C.D. (2008). Predicting the Brain Response to Treatment using a Bayesian Hierarchical Model with Application to a Study of Schizophrenia. *Human Brain Mapping*, 29(9), 1092-1106.
2. \*Chen, S. and Bowman, F. D. (2011). A Novel Support Vector Classifier for Longitudinal High-dimensional Data and Its Application to Neuroimaging Data. *Statistical Analysis and Data Mining*, 4(6): 604-611. PMID:25309639 [PubMed] PMCID:PMC4189187.
3. \*Derado, G., Bowman, F. D., and Zhang, L. (2013). Predicting Brain Activity using a Bayesian Spatial Model. *Statistical Methods in Medical Research*, 22(4):382-97. PMCID:PMC4175991.
4. \*Chen, S., Grant, E., Wu, T., Bowman, F.D. (2014). Statistical learning methods for longitudinal high-dimensional data. Wiley Interdisciplinary Reviews: *Computational Statistics*, 6:10–18. PMID:25285184 [PubMed] PMCID: PMC4181610.

### Longitudinal Data Methods

I have longstanding expertise in modeling longitudinal data, which I have built upon throughout my career. The prediction models described previously all involve longitudinal data. In addition, I have developed methods for longitudinal data focusing on statistical power, missing data, and joint modeling, among others. Missing data pose a threat to having adequate statistical power. We developed an approach that performs sample size calculations and power analyses, accounting for missing data by using a probabilistic framework to model the missing data mechanism (Bowman, 2004). In other work, we developed an approach to model longitudinal data jointly with a risk profile, permitting subsequent consideration of conditional models stratified by risk characteristics (Bowman and Manatunga, 2005). More recent work focuses on longitudinal imaging data.

1. \*Bowman, F. D. (2004). Predicting Power for Longitudinal Studies with Attrition, *Biometrical Journal* 46(4): 453-459.
2. \*Bowman, F. D. and Manatunga, A. (2005). A Joint Model for Longitudinal Data Profiles and Associated Event Risks with Application to a Depression Study. *Journal of the Royal Statistical Society, Series C, Applied Statistics* 54(2): 301-316.
3. Guo, Y. and Bowman, F. D. (2008). Modeling Dose-Dependent Neural Processing Responses Using Mixed Effects Spline Models. *NeuroImage*, 40: 698–711.
4. Lyles, R., Manatunga, A., Moore, R., and Bowman F. D. (2007). Improving point predictions of random effects for subjects at high-risk, *Statistics in Medicine* 26: 1285–1300. PMID:16810716

### **Complete List of Published Work in MyBibliography:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/f..bowman.1/bibliography/41156957/public/?sort=date&direction=ascending>

## D. Research Support

### Ongoing Research Support:

5 U18 NS082143-02 Bowman (PI) 09/30/12-08/31/16

NIH/NINDS

Analytic Methods for Determining Multimodal Biomarkers for Parkinson's Disease

This project develops novel statistical methods to identify multimodal biomarkers of Parkinson's disease using neuromelanin-MRI, DTI, resting-state fMRI, genotype information, and clinical variables.

Role: PI

### Completed Research Support (past 3 years):

5 R21 MH098212-02 Jovanovic (PI) 09/19/12-05/31/14

NIH/NIMHS

Neuroimaging Correlates of Impaired Fear Inhibition in PTSD

This study uses MRI and functional MRI to examine differences in PTSD related to impaired fear inhibition.

Role: Co-Investigator

5 T32 GM074909-08 Waller (PI) 07/04/05-06/30/13

NIH/NIGMS

Biostatistics in Genetics, Immunology, and Neuroimaging

This grant provides Ph.D. students in Biostatistics the opportunity to develop statistical and computational skills applied in genetics, immunology, or neuroimaging. Dr. Bowman directs training and research activities for the neuroimaging core.

Role: Neuroimaging Director

2 T15 HL098122-04 Waller (PI) 08/20/09-02/28/16 (effort on grant ended)

NIH/NHLBI

Atlanta Summer Institute for Training in Biostatistics

The Summer Institute for Training in Biostatistics (SIBS) is a program for undergraduate and graduate students who are interested in statistics, mathematics or science, and who want to learn about the field of biostatistics. Students engage in a comprehensive program of coursework, field experiences, hands-on data collection and analysis activities, and interactions with researchers and scientists in the fields of medicine and public health. Students also learn about graduate school and career opportunities in biostatistics.

Role: Co-Investigator

George Dalmida (PI) 02/01/13-10/31/15 (effort on grant ended)

NSF

Neuro-Biocultural Correlates of Sexual Risk Behavior (SRB) of Black Mid-Adolescent Girls

This project tests specific components of the Biopsychosocial Model of Risk Taking to understand the role of and relationships between endogenous (brain structure and function, hormones) and exogenous sociocultural factors (*i.e.* culture, ethnic identity, peer norms, parent factors) that may affect adolescent SRB.

Role: Co-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 FIVE PAGES.**

---

NAME: Stephan, Klaas

---

era COMMONS USER NAME (credential, e.g., agency login):

---

POSITION TITLE: Professor of Biomedical Engineering; Director of Translational Neuromodeling Unit

---

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

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INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Auguste Viktoria School, Itzehoe	B.S.	05/92	Mathematics
Heinrich-Heine-University Dusseldorf, Dusseldorf	M.D.	03/01	
Newcastle University, Newcastle	PHD	03/07	Neuroimaging and Neuroinformatics
Wellcome Trust Centre for Neuroimaging, University College London, London	Postdoctoral Fellow	12/07	Functional Neuroimaging

**A. Personal Statement**

My work is primarily concerned with the development and validation of mathematical models that infer subject-specific mechanisms of brain disease from non-invasive measures of neuronal activity and behavior. By developing such “computational assays” for quantifying individual physiological and computational principles underlying maladaptive cognition, I hope to contribute new diagnostic tools to psychiatry and neurology. The long-term goal is to establish these computational assays as a basis for formal differential diagnosis, pathophysiologically interpretable diagnostic classifications and individual treatment predictions.

I believe my research experience and qualification makes me ideal to play a role as a consultant in the present application. The propose K award application aligns well with my research program. The training plan detailed in this application will give Dr. Jiook Cha the necessary tools and expertise to become a pediatric neuroimager committed to studying effects of pathological anxiety on developmental trajectories of the corticolimbic function and connectivity. As a consultant, I will provide technical and scientific consultation on computational modeling of maladaptive threat processing (i.e., fear generalization) and model-based fMRI approach. This combination is deemed to help delineate underlying cognitive mechanisms (e.g., associative learning) using neurobehavioral data and use the model estimates to inform psychiatric diagnostic tools.

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

- 2001 - 2003 House Officer, Institute of Medicine, Research Center Julich, the University Hospital Aachen, Aachen
- 2003 - 2003 Research Fellow, Institute of Medicine, Research Centre Julich
- 2005 - 2007 Senior Research Fellow, Wellcome Trust Centre for Neuroimaging, London
- 2008 - Honorary Principal of Wellcome Trust Centre for Neuroimaging, University College london, London
- 2008 - 2010 Assistant Professor for Computational Neuroeconomics, Department of Economics, University of Zurich, Zurich
- 2010 - 2011 Associate Professor for Computational Neuroeconomics, Department of Economics, University of Zurich, Zurich
- 2011 - Professor of Translational Neuromodeling, University of Zurich & ETH Zurich, Zurich

- 2011 - Founding Director, Translational Neuroimaging Unit, University of Zurich & ETH Zurich, Zurich  
2014 - External Scientific Member, Max Planck Society, Cologne

### **Other Experience and Professional Memberships**

- Member, Swiss Society of Neuroscience
- Member, Society for Neuroscience
- Member, Organization of Human Brain Mapping (OHBM)

### **Honors**

- 1997 Scholar of the German National Academic Foundation, German National Academic Foundation  
1999 Scholar of the EU Advanced Course in Computational Neuroscience , Trieste, Italy  
2003 Wellcome Trust Travelling Research Fellow, Wellcome Trust  
2003 NeuroVisionen Award , Ministry of Science & Research, North Rhine-Westfalia  
2003 Dissertation Award , Medical Faculty of the Heinrich-Heine-University Düsseldorf  
2012 Wiley Young Investigator Award in Human Brain Mapping , Organization of Human Brain Mapping (OHBM)  
2014 External Scientific Member , the Max Planck Society

### **C. Contribution to Science**

1. Development of “computational assays”: computational modeling techniques for inferring on connectivity, synaptic plasticity and neuromodulation from fMRI and EEG data, e.g. dynamic causal modeling (DCM), Bayesian model selection (BMS), and model-based decoding.
  - a. Stephan KE, Weiskopf N, Drysdale PM, Robinson PA, Friston KJ. Comparing hemodynamic models with DCM. *Neuroimage*. 2007 Nov 15;38(3):387-401. PubMed PMID: [17884583](#); PubMed Central PMCID: [PMC2636182](#).
  - b. Moran RJ, Stephan KE, Kiebel SJ, Rombach N, O'Connor WT, Murphy KJ, Reilly RB, Friston KJ. Bayesian estimation of synaptic physiology from the spectral responses of neural masses. *Neuroimage*. 2008 Aug 1;42(1):272-84. PubMed PMID: [18515149](#); PubMed Central PMCID: [PMC2644419](#).
  - c. Stephan KE, Penny WD, Daunizeau J, Moran RJ, Friston KJ. Bayesian model selection for group studies. *Neuroimage*. 2009 Jul 15;46(4):1004-17. PubMed PMID: [19306932](#); PubMed Central PMCID: [PMC2703732](#).
  - d. Bernal-Casas D, Balaguer-Ballester E, Gerchen MF, Iglesias S, Walter H, Heinz A, Meyer-Lindenberg A, Stephan KE, Kirsch P. Multi-site reproducibility of prefrontal-hippocampal connectivity estimates by stochastic DCM. *Neuroimage*. 2013 Nov 15;82:555-63. PubMed PMID: [23747286](#).
2. Experimental and computational modeling (e.g., Hierarchical Gaussian Filter or **HGF**) studies of individual mechanisms underlying (mal)adaptive learning and decision-making.
  - a. Mathys CD, Lomakina EI, Daunizeau J, Iglesias S, Brodersen KH, Friston KJ, Stephan KE. Uncertainty in perception and the Hierarchical Gaussian Filter. *Front Hum Neurosci*. 2014;8:825. PubMed PMID: [25477800](#); PubMed Central PMCID: [PMC4237059](#).
  - b. Paliwal S, Petzschner FH, Schmitz AK, Tittgemeyer M, Stephan KE. A model-based analysis of impulsivity using a slot-machine gambling paradigm. *Front Hum Neurosci*. 2014;8:428. PubMed PMID: [25071497](#); PubMed Central PMCID: [PMC4080386](#).
  - c. Diaconescu AO, Mathys C, Weber LA, Daunizeau J, Kasper L, Lomakina EI, Fehr E, Stephan KE. Inferring on the intentions of others by hierarchical Bayesian learning. *PLoS Comput Biol*. 2014 Sep;10(9):e1003810. PubMed PMID: [25187943](#); PubMed Central PMCID: [PMC4154656](#).

- d. Vossel S, Bauer M, Mathys C, Adams RA, Dolan RJ, Stephan KE, Friston KJ. Cholinergic stimulation enhances Bayesian belief updating in the deployment of spatial attention. *J Neurosci*. 2014 Nov 19;34(47):15735-42. PubMed PMID: [25411501](#); PubMed Central PMCID: [PMC4236403](#).
3. Systematic model validation in physiological, pharmacological and patient studies.
  - a. Rowe J, Stephan KE, Friston K, Frackowiak R, Lees A, Passingham R. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. *Brain*. 2002 Feb;125(Pt 2):276-89. PubMed PMID: [11844728](#).
  - b. Manjaly ZM, Marshall JC, Stephan KE, Gurd JM, Zilles K, Fink GR. In search of the hidden: an fMRI study with implications for the study of patients with autism and with acquired brain injury. *Neuroimage*. 2003 Jul;19(3):674-83. PubMed PMID: [12880798](#).
  - c. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. *Biol Psychiatry*. 2006 May 15;59(10):929-39. PubMed PMID: [16427028](#).
  - d. Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ. Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. *J Neurosci*. 2006 Nov 1;26(44):11501-9. PubMed PMID: [17079679](#); PubMed Central PMCID: [PMC2635565](#).
4. Translation into clinical applications: Model-based diagnostic classifications that are pathophysiological interpretable and allow for individual treatment predictions.
  - a. Brodersen KH, Schofield TM, Leff AP, Ong CS, Lomakina EI, Buhmann JM, Stephan KE. Generative embedding for model-based classification of fMRI data. *PLoS Comput Biol*. 2011 Jun;7(6):e1002079. PubMed PMID: [21731479](#); PubMed Central PMCID: [PMC3121683](#).
  - b. Schmidt A, Smieskova R, Aston J, Simon A, Allen P, Fusar-Poli P, McGuire PK, Riecher-Rössler A, Stephan KE, Borgwardt S. Brain connectivity abnormalities predating the onset of psychosis: correlation with the effect of medication. *JAMA Psychiatry*. 2013 Sep;70(9):903-12. PubMed PMID: [23824230](#).
  - c. Brodersen KH, Deserno L, Schlagenhauf F, Lin Z, Penny WD, Buhmann JM, Stephan KE. Dissecting psychiatric spectrum disorders by generative embedding. *Neuroimage Clin*. 2014;4:98-111. PubMed PMID: [24363992](#); PubMed Central PMCID: [PMC3863808](#).

#### **Complete List of Published Work in My Bibliography:**

[http://www.ncbi.nlm.nih.gov/pubmed/?term=\(stephan+KE%5Bauthor%5D\)](http://www.ncbi.nlm.nih.gov/pubmed/?term=(stephan+KE%5Bauthor%5D))

#### **D. Research Support**

##### **Ongoing Research Support**

2014-2017

German Research Council (DFG)

Stephan, Klaas (PI)

Ingestive Behaviour: Homeostasis and Reward

Role: CPI

2014-2016

Swiss National Centre of Competence in Research (NCCR)

Stephan, Klaas (PI)

Developing novel high resolution fMRI methods for clinical neuroimaging

Role: PI

2014-2016

SystemsX.ch, The Swiss Initiative in Systems Biology

Stephan, Klaas (PI)

Prediction error processing in neural networks of the mammalian brain

Role: Co-Investigator

### **Completed Research Support**

2012-2015

Clinical Research Priority Program, University of Zurich

Stephan, Klaas (PI)

Multiple Sclerosis

Role: Co-Investigator

2014

COMPASS-APS, Baugarten Foundation, Zurich, 2014

Stephan, Klaas (PI)

Project Grant

Role: PI

2011-2013

European Union FP7

Stephan, Klaas (PI)

Dopaminergic modulation of plasticity during social learning

Role: PI

2012-2013

SystemsX.ch, The Swiss Initiative in Systems Biology

Stephan, Klaas (PI)

Neurochoice: neural correlates of collective decision making

Role: CPI

**BIOGRAPHICAL SKETCH**

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

NAME: Yoo, Shinjae

ERA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Associate Scientist

**EDUCATION/TRAINING** (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Soongsil University, Seoul	BS	02/2000	Computer Science
Seoul National University, Seoul	MS	02/2002	Computer Science
Carnegie Mellon University, Pittsburgh, PA Carnegie Mellon University, Pittsburgh	MS	05/2005	Text Mining
Carnegie Mellon University, Pittsburgh, PA Carnegie Mellon University, Pittsburgh	PhD	06/2010	Text Mining

**A. Personal Statement**

I will be supervising the application of advanced computational methods to neuroimaging data as described in the training plan. This includes state-of-the-art predictive modeling using machine learning algorithms (e.g. Manifold Learning, Bayesian Graphical Modeling, Semi-supervised Network Analysis, etc.) that I have developed or applied. Previously these algorithms have been successfully applied social network analysis, genetics (bioinformatics), solar energy, and X-ray scattering. As a data scientist, I have worked with domain scientists in a wide range of fields. Despite that neuroimaging can tremendously benefit from application of these cutting edge machine learning algorithms, compared with other data-intensive fields, such attempts have been only scarcely made in neuroimaging and psychiatric research. It is therefore of a tremendous interest Dr. Cha's application of this advanced computational approach to multimodal neuroimaging data. Our approach could potentially improve both sensitivity and specificity of neuroimaging measures so that they can be used for early detection of brain abnormalities. My experience and qualifications make me well-suited for this role on this application.

1. Yoo S, Yang Y, Lin F, Moon I. Mining Social Networks for Personalized Email Prioritization. ACM SIGKDD Conference on Knowledge Discovery and Data Mining (KDD); 2009.
2. Huang H, Yoo S, Kaznatcheev K, Yager K, Lu F, Yu D, Gang O, Qin H. Diffusion-based Clustering Analysis of Coherent X-ray Scattering Patterns of Self-assembled Nanoparticles. ACM Symposium on Applied Computing (SAC); 2014.
3. Huang H, Yoo S, Yu D, Qin H. Diverse Power Iteration Embeddings and Its Applications. IEEE International Conference on Data Mining (ICDM); 2014.
4. Xu J, Yoo S, Yu D, Huang H, Huang D, Heiser J, Kalb P. A Stochastic Framework for Solar Irradiance Forecasting Using Conditional Random Field. PAKDD; 2015.

## B. Positions and Honors

### Positions and Employment

2010 - 2011 Research Associate, Computational Science Center, Brookhaven National Lab., Upton, NY  
2011 - 2013 Assistant Scientist, Computational Science Center, Brookhaven National Lab., Upton, NY  
2013 - Associate Scientist, Computational Science Center, Brookhaven National Lab., Upton, NY  
2014 - Adjunct Assistant Professor, Institute for Advanced Computational Science, Stony Brook University, Stony Brook, NY

### Other Experience and Professional Memberships

2010 - Member, ACM Special Interest Group for Knowledge Discovery and Data Mining  
2012 - Member, International Society for Computational Biology  
2013 - Member, Association for Computing Machinery (ACM)

## C. Contribution to Science

1. Unsupervised learning is trying to find interesting pattern of data or reducing dimension without any human labeled data. A robust learning is especially important for the unsupervised learning because we are trying to discover novel things from unknown distributions. We proposed to apply diffusion kernels, better normalization, and harmonic operators on clustering and anomaly detections and showed robust clustering analysis and superb anomaly detection results. Especially, our proposed anomaly detection algorithms find not only global anomalies but also local anomalies where local anomalies are quite different from their local neighborhood. Those robust learning algorithms are very general and it can be easily applicable to various health science applications. I supervised one student and co-developed the algorithms.
  - a. Huang H, Yoo S, Qin H, Yu D. A Robust Clustering Algorithm Based on Aggregated Heat Kernel Mapping. IEEE International Conference on Data Mining (ICDM); 2011.
  - b. Huang H, Yoo S, Yu D, Qin H. Noise-Resistant Unsupervised Feature Selection via Multi-Perspective Correlations. IEEE International Conference on Data Mining (ICDM); 2014.
  - c. Huang H, Qin H, Yoo S, Yu D. Physics-based Anomaly Detection Defined on Manifold Space. ACM Transactions on Knowledge Discovery from Data (TKDD). 2014 September; 9(2).
  - d. Huang H, Yoo S, Yu D, Qin H. Density-aware Clustering based on Aggregated Heat Kernel and Its Transformation. ACM Transactions on Knowledge Discovery from Data (TKDD). Forthcoming;
2. The curse of dimensionality hinders discovering the salient signal out of data and causes the inefficiencies in learning algorithms. Manifold learning reveals the intrinsic information from high dimensional space but suffer seriously due to quadratic space and cubic time complexities. We propose the power iteration based approximation of diffused manifold space, which ensures 1000 times speed up and does not require quadratic spaces, so that we could enjoy the power of manifold learning without burdens. My ongoing research showed that we can even approximate such manifold learning with read only once, limited memory, and limited processing capability (streaming algorithm). Such approximations is the key enabler for big data science if we have to handle multimodal analysis. I supervised one student and co-developed the algorithms.
  - a. Huang H, Yoo S, Yu D, Qin H. Diverse Power Iteration Embeddings and Its Applications. IEEE International Conference on Data Mining (ICDM); 2014.

3. Solar energy is one of the most promising renewable energy source but the power generation is too sensitive to the cloud distribution, so that it is difficult to be integrated into power grid system. Although the sky image is the best resource to predict, the sky imager itself is limited scope. To enhance solar energy prediction, we integrated multiple sky images, satellite images, or numerical weather predictions. Such multimodal approaches significantly improved prediction accuracies. Combining diverse source of information in other science and health domain is the key to the success. I supervised two students and co-developed algorithms.
    - a. Peng Z, Yoo S, Yu D, Huang D. Solar Irradiance Forecast System Based on Geostationary Satellite. IEEE SmartGridComm; 2013.
    - b. Peng Z, Yoo S, Yu D, Huang D, Kalb P, Heiser J. 3D Cloud Detection and Tracking for Solar Forecast using Multiple Sky Imagers. ACM Symposium on Applied Computing (SAC); 2014.
    - c. Xu J, Yoo S, Yu D, Huang H, Huang D, Heiser J, Kalb P. A Stochastic Framework for Solar Irradiance Forecasting Using Conditional Random Field. PAKDD; 2015.
    - d. Xu J, Yoo S, Yu D, Huang D, Heiser J, Kalb P. Solar Irradiance Forecasting using Multi-layer Cloud Tracking and Numerical Weather Prediction. ACM Symposium on Applied Computing (SAC); 2015.
  4. To overcome information overload, personally interested and important information filtering is critical. However, personalized learning faces serious lack of training data. I proposed to combine implied social networks into email stream filtering task and significantly improve prediction accuracy with very small number of training data. The amount of individual study data may not be big enough but if we combine the rich background information, it can significantly improve the scientific and medical study analysis.
    - a. Yang Y, Yoo S, Zhang J, Kisiel B. Robustness of adaptive filtering methods in a cross-benchmark evaluation. ACM SIGIR; 2005.
    - b. Yoo S, Yang Y, Lin F, Moon I. Mining Social Networks for Personalized Email Prioritization. ACM SIGKDD Conference on Knowledge Discovery and Data Mining (KDD); 2009.
    - c. Yang Y, Yoo S, Lin F, Moon I. Personalized email prioritization based on content and social network analysis. IEEE Intelligent Systems: Special Issue on Social Learning. 2010 July; 25(4):12-18.
    - d. Yoo S, Yang Y, Carbonell J. Modeling Personalized Email Prioritization: Classification-based and Regression-based Approaches. ACM Conference on Information and Knowledge Management (CIKM); 2011.
- **Complete List of Published Work in My Bibliography:**  
[https://scholar.google.com/scholar?start=10&q=author%3A%22Shinjae+Yoo%22&hl=en&as\\_sdt=0,33](https://scholar.google.com/scholar?start=10&q=author%3A%22Shinjae+Yoo%22&hl=en&as_sdt=0,33)

## D. Research Support

### Ongoing Research Support

2011/10/01-2015/09/30

DE-AC02-98CH10886, DOE BER (Basic Energy Research) Sergei Maslov (PI)

DOE Systems Biology KBase

Role: KP

**CURRENT & PENDING SUPPORT FOR MENTORS/CO-MENTORS****Jonathan Posner**

Dr. Posner has an appointment at the New York State Psychiatric Institute/Research Foundation for Mental Hygiene and Columbia University. This is detailed in a Dual Appointment Agreement between the entities and precludes the possibility of NYSPI/RFMH supporting effort supported by Columbia University and vice versa. Therefore, each project listed below indicates effort at each institution and also Total Professional Effort ('TPE') encompassing the multiple appointments.

**RFMH Active**

T32 MH096679 (Attia/Walsh)	6/1/2013 - 5/31/2018	0.60 CM
NIMH	\$197,094	TPE 0.47 CM

Research Training in Biobehavioral Disturbances of Eating Disorders

This postdoctoral training grant supports clinician scientists interested in becoming independent investigators focusing on eating disorders.

Role: Fellow Primary Mentor

Effort on this project is donated from Dr. Posner's NY State line.

P50 MH090966 (Gingrich)	9/1/2010 - 4/30/2016 (NCE)	2.04 CM
NIMH	\$2,185,682	TPE 1.80 CM

Serotonergic Modulation of Brain Development: Genetic and Pharmacologic Influences on Structure, Function, and Behavior

This study aims to determine whether low-expressing 5htlpr 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 Imaging Core

Effort on this project is donated from Dr. Posner's NY State line.

R01 MH104648 (Marsh/Simpson)	9/19/2014 - 5/31/2018	0.68 CM
NIMH	\$465,940	TPE 0.60 CM

Control and Reward Circuits as Targets for Repetitive Thoughts and Behaviors

The study aims to examine neural circuits underlying cognitive control and reward processing in adults with repetitive thoughts and behaviors.

Role: Co-Investigator

Effort on this project is donated from Dr. Posner's NY State line.

R01 MH101172 (Posner)	8/16/2013 - 1/31/2018	4.42 CM
NIMH	\$364,365	TPE 3.90 CM

Imaging Stimulant Effects on Emotional Lability in Children with ADHD

The purpose of this study is to examine the neural mechanisms by which stimulant

Role: Principal Investigator

R21 MH099388 (Steinglass/Posner) 1/13/2014 - 12/31/2016 2.21 CM  
 NIMH \$193,403 TPE 1.95 CM  
 Multimodal Imaging of the Mesocortical System in Anorexia Nervosa  
 The purpose of this study is to examine the functional and structural connectivity of the mesocortical system in individuals with Anorexia Nervosa.  
 Role: Co-Principal Investigator

R01 MH036197 (Weissman) 7/1/87 - 1/31/2017 1.36 CM  
 NIMH \$738,965 TPE 1.20 CM  
 Children at High and Low Risk for Depression  
 The purpose of this study is to use MRI to identify biological vulnerability for depression based on a 3-generation study of families at high and low risk for Major Depressive Disorder.  
 Role: Co-Investigator

### RFMH Pending

R01 (Posner/Steinglass) NIMH 7/1/2016 - 6/30/2021 \$487,863 3.96 CM  
 NIMH \$487,863 TPE 3.08 CM  
 Longitudinal Assessment of Neural Circuits in Adolescents with Anorexia Nervosa  
 This project will examine reward and habit neural circuits in adolescents with Anorexia.  
 Role: Co-Principal Investigator

R01 (Weissman/Posner) 7/1/2016 - 6/30/2019 2.40 CM  
 NIMH \$497,000 TPE 1.87 CM  
 Children at High and Low Risk for Depression (Renewal)  
 The purpose of this study is to use MRI to identify biological vulnerability for depression based on a 3-generation study of families at high and low risk for Major Depressive Disorder.  
 Role: Co-Investigator

If any of the above pending grants are funded, Dr. Posner will adjust his effort appropriately with agency program staff so as not to exceed 100% effort (12.0 CM TPE).

### Columbia University Active

Foundation Grant (Posner) 7/1/2015 - 6/30/2016 \$100,000 1.11 CM  
 St. Baldrick's Foundation \$100,000 TPE 0.54 CM  
 Biological Substrates of Impaired Neurocognitive Functioning  
 The aim of this study is to identify the alterations in functional and structural brain connectivity that correlate with neurocognitive decline by collecting advanced magnetic resonance imaging (MRI) and neuropsychological test data on survivors of pediatric brain tumors.  
 Role: Principal Investigator

54679 (Weissman) 1/1/2015 - 12/31/2017 0.15 CM  
 John Templeton Foundation \$493,724 TPE 0.07 CM  
 Understanding the Role of Belief in the Resilience of Families at Risk for Depression: Religion, Brain structure and Function  
 The study aims to understand biological markers that are protective against the development of depression.  
 Role: Co-Investigator

**CURRENT & PENDING SUPPORT FOR MENTORS/CO-MENTORS****Helen Blair Simpson**

Dr. Simpson has an appointment at the New York State Psychiatric Institute/Research Foundation for Mental Hygiene and Columbia University. This is detailed in a Dual Appointment Agreement between the entities and precludes the possibility of NYSPI/RFMH supporting effort supported by Columbia University and vice versa. Therefore, each project listed below indicates effort at each institution and also Total Professional Effort ('TPE') encompassing the multiple appointments.

**RFMH Active**

R34 MH095502 (Rynn)	7/1/2012 - 4/30/2016	1.05 CM
NIMH	\$544,827	TPE 0.96 CM
Novel Medication Strategies to Target Brain Mechanisms in Pediatric OCD		
This study examines minocycline as a novel strategy for pediatric OCD		
Role: Co-Principal Investigator		
R01 M045436 (Simpson)	8/1/1990 - 6/30/2016	1.05 CM
NIMH	\$287,085	TPE 0.96 CM
Attaining and Maintaining Wellness in OCD		
This study examines whether adults with OCD who attain wellness after SRIs + EXRP can then maintain wellness		
Role: Principal Investigator		
R21 MH099388 (Steinglass, Posner)	1/13/2014 - 1/12/2017	0.13 CM
NIMH	\$45,000	TPE 0.12 CM
Multimodal Imaging in Anorexia Nervosa		
This project will use complementary neuroimaging techniques to study neural circuitry in anorexia nervosa.		
Using resting state functional neuroimaging, diffusion tension imaging, and arterial spin labeling, we will evaluate the mesocortical system in individuals with anorexia nervosa before and after weight regulation treatment, as compared with healthy controls.		
Role: Co-Investigator		

**RFMH Pending**

R01MH108364 (Simpson)	6/1/2016 - 5/31/2021	0.98 CM
NIMH	\$1,962,671	TPE 0.60 CM
Developing a Global Network to Advance Research on Obsessive-Compulsive Disorder		
This project will develop a global network for brain research on OCD.		
Role: Principal Investigator		

**Columbia University Active**

K99 MH106719 (Dunsmoor)	4/15/2015 - 3/31/2017	0.60 CM
NIMH	\$904,830	TPE 0.23 CM
Improving the Control of Fear: Healthy Adults to Pathological Anxiety		
Role: Mentor		

Effort on this Project is subsumed under Dr. Simpson's K24 Award.

R01 MH104648 (Marsh/Simpson) 9/19/2014 - 6/30/2018 2.91 CM  
NIMH \$116,665 TPE 1.12 CM  
Control and Reward Circuits as Targets for Repetitive Thoughts and Behaviors  
The goal of this project is to use multi-modal imaging to elucidate how abnormalities in cognitive control and reward circuits contribute to repetitive thoughts and behaviors.  
Role: Principal Investigator

K23 MH092434 (Rodriguez) 4/1/2011 - 6/30/2016 0.60 CM  
NIMH \$171,500 TPE 0.23 CM  
Novel Interventions for Adults with OCD  
The award enables the PI to pursue a training and research program in OCD and related disorders.  
Role: Mentor

Effort on this Project is subsumed under Dr. Simpson's K24 Award.

K24 MH091555 (Simpson) 9/1/2010 - 2/28/2016 7.34 CM  
NIMH \$63,429 TPE 1.00 CM  
Enhancing Patient Oriented Research and Training in OCD  
This project supports Dr. Simpson's mentoring and training activities.  
Role: Principal Investigator

R01 MH045436 (Walsh/Simpson) 8/1/1990 - 6/30/2016 \$63,429 1.75 CM  
NIMH \$63,429 TPE 1.00 CM  
Attaining and Maintaining Wellness in OCD  
This study examines whether adults with OCD who attain wellness after SRIs + EXRP can then maintain wellness.  
Role: Principal Investigator

### Columbia University Pending

R01 MH108364 (Simpson) 6/1/2016 - 5/31/2021 4.32 CM  
NIMH \$368,402 TPE 1.66 CM  
Developing a Global Network to Advance Research on Obsessive-Compulsive Disorder  
This project will develop a global network for brain research on OCD.  
Role: Co-Investigator

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, Budget Period 1

ORGANIZATIONAL DUNS\*: 1672049940000

**Budget Type\***:   ● Project   ○ Subaward/Consortium**Enter name of Organization:** Research Foundation for Mental Hygiene, Inc.

Start Date\*: 09-01-2016

End Date\*: 08-31-2017

Budget Period: 1

**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Jiook		Cha		PD/PI	100,000.00	10.8			90,000.00	31,500.00	121,500.00

**Total Funds Requested for all Senior Key Persons in the attached file**

<b>Additional Senior Key Persons:</b>	File Name:	<b>Total Senior/Key Person</b>	<b>121,500.00</b>
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**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	6.1			15,631.00	5,471.00	21,102.00
<b>1</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>21,102.00</b>
						<b>Total Salary, Wages and Fringe Benefits (A+B)</b>	<b>142,602.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1****ORGANIZATIONAL DUNS\*:** 1672049940000**Budget Type\*:**  Project  Subaward/Consortium**Organization:** Research Foundation for Mental Hygiene, Inc.**Start Date\***: 09-01-2016**End Date\***: 08-31-2017**Budget Period:** 1

<b>C. Equipment Description</b>	
List items and dollar amount for each item exceeding \$5,000	
<b>Equipment Item</b>	<b>Funds Requested (\$)*</b>
<b>Total funds requested for all equipment listed in the attached file</b>	<hr/>
	<b>Total Equipment</b>
<b>Additional Equipment:</b> File Name:	

<b>D. Travel</b>		<b>Funds Requested (\$)*</b>
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)		2,000.00
2. Foreign Travel Costs		<hr/>
<b>Total Travel Cost</b>		<b>2,000.00</b>

<b>E. Participant/Trainee Support Costs</b>		<b>Funds Requested (\$)*</b>
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
<b>Number of Participants/Trainees</b>		<b>Total Participant Trainee Support Costs</b>

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

**RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1****ORGANIZATIONAL DUNS\*:** 1672049940000**Budget Type\*:** ● Project ○ Subaward/Consortium**Organization:** Research Foundation for Mental Hygiene, Inc.**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 1

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	2,778.00
2. Publication Costs	3,000.00
3. Consultant Services	
4. ADP/Computer Services	1,059.00
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Costs	20,060.00
	<b>Total Other Direct Costs</b>
	<b>26,897.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
	<b>Total Direct Costs (A thru F)</b>
	<b>171,499.00</b>

<b>H. Indirect Costs</b>	<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
	1 . Modified TDC	8	171,499.00	13,720.00
	<b>Total Indirect Costs</b>			
	<b>13,720.00</b>			
<b>Cognizant Federal Agency</b>	DHHS, Ryan McCarthy, (212) 264-2069			
(Agency Name, POC Name, and POC Phone Number)				

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
	<b>Total Direct and Indirect Institutional Costs (G + H)</b>
	<b>185,219.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>

<b>K. Budget Justification*</b>	File Name: FINAL1454.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, Budget Period 2

ORGANIZATIONAL DUNS\*: 1672049940000

**Budget Type\***:   ● Project   ○ Subaward/Consortium**Enter name of Organization:** Research Foundation for Mental Hygiene, Inc.

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 2

**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Jiook		Cha		PD/PI	100,000.00	10.8			90,000.00	31,500.00	121,500.00

**Total Funds Requested for all Senior Key Persons in the attached file**

<b>Additional Senior Key Persons:</b>	File Name:	<b>Total Senior/Key Person</b>	<b>121,500.00</b>
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**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	6.1			16,100.00	5,635.00	21,735.00
<b>1</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>21,735.00</b>
					<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>143,235.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2****ORGANIZATIONAL DUNS\*:** 1672049940000**Budget Type\*:**  Project  Subaward/Consortium**Organization:** Research Foundation for Mental Hygiene, Inc.**Start Date\***: 09-01-2017**End Date\***: 08-31-2018**Budget Period:** 2

<b>C. Equipment Description</b>	
List items and dollar amount for each item exceeding \$5,000	
<b>Equipment Item</b>	<b>Funds Requested (\$)*</b>
<b>Total funds requested for all equipment listed in the attached file</b>	<b>Total Equipment</b>
<b>Additional Equipment:</b> File Name:	

<b>D. Travel</b>		<b>Funds Requested (\$)*</b>
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)		2,000.00
2. Foreign Travel Costs		
<b>Total Travel Cost</b>		<b>2,000.00</b>

<b>E. Participant/Trainee Support Costs</b>		<b>Funds Requested (\$)*</b>
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
<b>Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	

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

**RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2****ORGANIZATIONAL DUNS\*:** 1672049940000**Budget Type\*:** ● Project ○ Subaward/Consortium**Organization:** Research Foundation for Mental Hygiene, Inc.**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 2

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	1,653.00
2. Publication Costs	3,000.00
3. Consultant Services	
4. ADP/Computer Services	1,101.00
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Costs	20,510.00
	<b>Total Other Direct Costs</b>
	<b>26,264.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
	<b>Total Direct Costs (A thru F)</b>
	<b>171,499.00</b>

<b>H. Indirect Costs</b>	<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
	1 . Modified TDC	8	171,499.00	13,720.00
	<b>Total Indirect Costs</b>			
	<b>13,720.00</b>			
<b>Cognizant Federal Agency</b>	DHHS, Ryan McCarthy, (212) 264-2069			
(Agency Name, POC Name, and POC Phone Number)				

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
	<b>Total Direct and Indirect Institutional Costs (G + H)</b>
	<b>185,219.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>

<b>K. Budget Justification*</b>	File Name: FINAL1454.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, Budget Period 3

ORGANIZATIONAL DUNS\*: 1672049940000

**Budget Type\***:   ● Project   ○ Subaward/Consortium**Enter name of Organization:** Research Foundation for Mental Hygiene, Inc.

Start Date\*: 09-01-2018

End Date\*: 08-31-2019

Budget Period: 3

**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Jiook		Cha		PD/PI	100,000.00	10.8			90,000.00	31,500.00	121,500.00

**Total Funds Requested for all Senior Key Persons in the attached file**

<b>Additional Senior Key Persons:</b>	File Name:	<b>Total Senior/Key Person</b>	<b>121,500.00</b>
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**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	5.45			14,816.00	5,186.00	20,002.00
<b>1</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>20,002.00</b>
					<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>141,502.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3****ORGANIZATIONAL DUNS\*:** 1672049940000**Budget Type\*:**  Project  Subaward/Consortium**Organization:** Research Foundation for Mental Hygiene, Inc.**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 3**C. Equipment Description**

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

**Equipment Item****Funds Requested (\$)\*****Total funds requested for all equipment listed in the attached file****Total Equipment****Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

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

2. Foreign Travel Costs

4,000.00

**Total Travel Cost****4,000.00****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 &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3****ORGANIZATIONAL DUNS\*:** 1672049940000**Budget Type\*:** ● Project ○ Subaward/Consortium**Organization:** Research Foundation for Mental Hygiene, Inc.**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 3

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	878.00
2. Publication Costs	3,000.00
3. Consultant Services	
4. ADP/Computer Services	1,145.00
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Costs	20,974.00
	<b>Total Other Direct Costs</b>
	<b>25,997.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
	<b>Total Direct Costs (A thru F)</b>
	<b>171,499.00</b>

<b>H. Indirect Costs</b>	<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
	1 . Modified TDC	8	171,498.00	13,720.00
	<b>Total Indirect Costs</b>			
	<b>13,720.00</b>			
<b>Cognizant Federal Agency</b>	DHHS, Ryan McCarthy, (212) 264-2069			
(Agency Name, POC Name, and POC Phone Number)				

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
	<b>Total Direct and Indirect Institutional Costs (G + H)</b>
	<b>185,219.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>

<b>K. Budget Justification*</b>	File Name: FINAL1454.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, Budget Period 4

ORGANIZATIONAL DUNS\*: 1672049940000

**Budget Type\***:   ● Project   ○ Subaward/Consortium**Enter name of Organization:** Research Foundation for Mental Hygiene, Inc.

Start Date\*: 09-01-2019

End Date\*: 08-31-2020

Budget Period: 4

**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Jiook		Cha		PD/PI	100,000.00	10.8			90,000.00	31,500.00	121,500.00

**Total Funds Requested for all Senior Key Persons in the attached file**

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	121,500.00
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**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	5.57			15,597.00	5,459.00	21,056.00
1	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>21,056.00</b>
					<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>142,556.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4****ORGANIZATIONAL DUNS\*:** 1672049940000**Budget Type\*:**  Project  Subaward/Consortium**Organization:** Research Foundation for Mental Hygiene, Inc.**Start Date\***: 09-01-2019**End Date\***: 08-31-2020**Budget Period:** 4

<b>C. Equipment Description</b>	
List items and dollar amount for each item exceeding \$5,000	
<b>Equipment Item</b>	<b>Funds Requested (\$)*</b>
<b>Total funds requested for all equipment listed in the attached file</b>	<hr/>
	<b>Total Equipment</b>
<b>Additional Equipment:</b> File Name:	

<b>D. Travel</b>		<b>Funds Requested (\$)*</b>
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)		2,000.00
2. Foreign Travel Costs		<hr/> 2,000.00
<b>Total Travel Cost</b>		<b>4,000.00</b>

<b>E. Participant/Trainee Support Costs</b>		<b>Funds Requested (\$)*</b>
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
<b>Number of Participants/Trainees</b>		<b>Total Participant Trainee Support Costs</b>

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

**RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4****ORGANIZATIONAL DUNS\*:** 1672049940000**Budget Type\*:** ● Project ○ Subaward/Consortium**Organization:** Research Foundation for Mental Hygiene, Inc.**Start Date\*:** 09-01-2019**End Date\*:** 08-31-2020**Budget Period:** 4

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	1,192.00
2. Publication Costs	3,000.00
3. Consultant Services	
4. ADP/Computer Services	20,191.00
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Costs	560.00
<b>Total Other Direct Costs</b>	<b>24,943.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>171,499.00</b>

<b>H. Indirect Costs</b>	<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
	1 . Modified TDC	8	171,498.00	13,720.00
	<b>Total Indirect Costs</b>			
<b>Cognizant Federal Agency</b>	DHHS, Ryan McCarthy, (212) 264-2069			
(Agency Name, POC Name, and POC Phone Number)				

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>185,219.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>

<b>K. Budget Justification*</b>	File Name: FINAL1454.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## BUDGET JUSTIFICATION

### PERSONNEL

**Jiook Cha, PhD–Principal Investigator** (10.8 CM effort, salary support requested) is trained as a cognitive neuroscientist and as a Post-Doctoral Research Fellow in Child and Adolescent Psychiatry in the Department of Psychiatry at Columbia University Medical Center (CUMC) and The New York State Psychiatric Institute (NYSPI). In 2016, Dr. Cha will be appointed to Assistant Professor of Psychiatry in the Division of Child and Adolescent Psychiatry. Dr. Cha will devote 90% effort during years 01-04 of the K01 Mentored Research Career Development Award to the proposed training and research activities. He will be mentored by Drs. Posner (primary mentor) and Simpson, and advisors consisting of experts in various fields, including childhood anxiety disorders, translational neuroscience, and computational data analysis. Building on his core strengths in cognitive neuroscience and multimodal MRI, Dr. Cha's ultimate goal is to develop neuroimaging markers of anxiety disorders for better diagnosis, treatment response, and development of novel treatment. Towards this long-term ambition and for the successful transition to research independence, specific training goals for the 4-year period of this proposal are (1) Phenomenology of anxiety disorders; (2) Patient-oriented, translational and developmental neuroscience of anxiety; (3) Advanced computational neuroimaging; and (4) responsible conduct of research. During the award period, in parallel with his training plan, Dr. Cha will conduct mentored research designed to directly bridge these training goals. Specifically, he will investigate whether fear generalization occurs in youth and how pathological anxiety affects fear generalization and its neural correlates. Dr. Cha 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. Cha will work towards reporting findings from this and related studies in conference presentations and peer-reviewed articles.

**Jonathan Posner, MD–Mentor (no salary requested).** Dr. Posner is Associate Professor of Clinical Psychiatry, Director of the Pediatric Neuroimaging Laboratory in the Division of Child Psychiatry at CU/NYSPI. He has extensive experience in using pediatric neuroimaging to probe brain's emotional circuit in youths with various affective disorders. He has been a principal investigator on 3 NIH grants including NIMH K23, R01, and R21 awards, and is the project leader for a Multimodal Imaging Core within a Conte Center examining the effects of serotonergic modulation on brain development. This has led him to provide Dr. Cha with effective mentorship during his postdoctoral fellowship, evidenced by first-authored publications (three in review), a NARSAD Young Investigator award, three travel awards, and internal research grants. Therefore, in this K01 award, he will be an ideal mentor for Dr. Cha's career path to full independence. Dr. Posner has worked with Dr. Cha in the development of this proposed project thus far. In this proposal, Dr. Posner will mentor and supervise Dr. Cha's training in pediatric neuroimaging and translational, developmental neuroscience in studies of youth anxiety disorders.

**Helen Blair Simpson, MD, PhD–Co-Mentor (no salary requested).** Dr. Simpson is Professor of Psychiatry at CU/NYSPI and the Director of the Anxiety Disorders Clinic at the New York State Psychiatric Institute. Her research program is committed to transforming understanding of and treatments for anxiety and related disorders. Her interdisciplinary research ranges from treatment development studies to clinical trials examining the effects of medication and cognitive-behavioral therapy to brain imaging studies exploring the brain mechanisms of OCD to animal studies in collaboration with basic scientists. She is a member of the Working Group on the Classification of Obsessive Compulsive Disorders for the World Health Organization, and was charged with revising the diagnostic criteria for OCD. Dr. Simpson also participates in the Research Domain Criteria (RDoC) project at the National Institutes of Mental Health, first as a member of the Negative Valence Systems Workshop in 2011, and now as the Principal Investigator of an NIMH-grant consistent with the RDoC approach. She has been the principal investigator of multiple NIMH grants, including the current NIMH midcareer investigator award in Patient-Oriented Research (K24). Dr. Simpson has mentored numerous K-awardees, many of whom have successfully transitioned to independent researchers. Dr. Simpson has been directly involved in the conception of this application. In this proposal, Dr. Simpson will mentor and supervise Dr. Cha's training in adulthood anxiety disorders and translational neuroscience research.

**Moira Rynn, MD–Advisor & Collaborator (no salary requested).** Dr. Rynn is Ruane Professor of Psychiatry at CU/NYSPI and is the Division Chief of Child and Adolescent Psychiatry, Department of Psychiatry at CU/NYSPI. Dr. Rynn's area of research is focused on pediatric psychopharmacology with an emphasis on

anxiety disorders. Additionally, Dr. Rynn has been the co-Principal Investigator on the largest published study in pediatric anxiety disorders, the Child/Adolescent Anxiety Multimodal Treatment Study (CAMS, Walkup et al, 2008) and has published more than a dozen clinical trials in anxiety disorders. In this proposal, Dr. Rynn will supervise training in childhood anxiety disorders.

**Daniel Pine, MD–Advisor & Collaborator (no salary requested).** Dr. Pine is Chief of the Section on Development and Affective Neuroscience of the National Institute of Mental Health Intramural Research Program. He has been engaged continuously in research focusing on the epidemiology, biology and treatment of psychiatric disorders in children and adolescents. In particular, he has extensive expertise in application of translational and developmental neuroscience to studies of anxiety disorders in youth and has published more than 350 peer-reviewed manuscripts on these topics. In addition, he has been actively involved in explorations of development-related commonalities and differences among psychiatric disorders. Dr. Pine's research has also involved the use of novel fMRI paradigms to evaluate the brain circuitry of anxiety disorders in youth and various interventions on these fear networks in youths. In this proposal, Dr. Pine will provide hands-on training in psychophysiological and neuroimaging experiments with youths with anxiety disorders and supervise overall training in translational and developmental neuroscience.

**Dubois Bowman, PhD–Advisor & Collaborator (no salary requested).** Dr. Bowman is Chair of the Department of Biostatistics in Mailman School of Public Health at CUMC. Dr. Bowman is a renowned expert in the development and application of biostatistical methods for multimodal brain imaging data. His expertise in integration of multimodal MRI data to inform predictive modeling for diagnosis and treatment responses of mental disorders is particularly relevant to this proposal. His research has helped to reveal brain patterns that reflect disruption from psychiatric diseases; to determine biomarkers for neurological diseases; and to inform individualized therapeutic treatments. His work has important implications for mental and neurological health disorders such as depression, schizophrenia and Parkinson's disease. In this proposal, he will supervise training in the advanced computational methods to neuroimaging (Training Goal #3) and will review overall progress in this aspect.

**Klaas Enno Stephan, MD, PhD–Advisor & Collaborator (no salary requested).** Dr. Stephan is Professor of Translational Neuromodeling, at Institute for Biomedical Engineering, Director of Translational Neuromodeling Unit (TNU), at University of Zurich & ETH Zurich. His work focuses on developing “computational assays”, i.e., mathematical models for inferring neuronal mechanisms underlying mental diseases from non-invasive brain activity measurements in individual patients. Such assays will enable more precise diagnostics of disease mechanisms and individualized treatment recommendations, leading to a redefinition of mental diseases and a transformation of clinical practice. In 2012, Dr. Stephan founded the Translational Neuromodeling Unit (TNU), the first institution with the explicit mission statement to translate advances in computational neuroscience into diagnostic tools for clinical practice. At the TNU, computational scientists and clinicians jointly develop mathematical models of brain disease and evaluate their diagnostic use for psychiatry and neurology in patient studies. In this proposal, Dr. Stephan will serve as an advisor to provide hands-on training in a recently developed Bayesian modeling (Hierarchical Gaussian Filtering) to infer subject-specific learning processes underlying maladaptive threat processing. Compared with conventional learning models, the HGF is much flexible and sensitive to detect subtle differences across subjects' neurobehavioral timeseries data. Dr. Stephan will host Dr. Cha at TNU, Zurich, in Switzerland, to provide to learn the HGF application to the neurobehavioral data of fear generalization fMRI experiment.

**Shin-Jae Yoo, PhD–Advisor & Collaborator (no salary requested).** Dr. Yoo is Associate Computational Scientist at Brookhaven National Laboratory. As a data scientist, his research focuses on large-scale data mining in bioinformatics, nuclear physics, astronomy, climate science, and social network analysis. Drs. Yoo and Cha, together with Dr. Posner, a project leader for a Multimodal Imaging Core within a Conte Center at CUMC, have been collaborating on application of big-data science approach to brain connectivity data to examine the effects of serotonergic modulation on brain development. In this proposal, serving as an advisor for advanced computational methods to neuroimaging, Dr. Yoo will provide hands-on training in the application of machine learning algorithms and network analysis to connectivity data generated from diffusion and resting-state functional MRI.

**YEAR 1****PERSONNEL**

**Research Assistant (6.1 CM effort):** Salary is requested for a part-time, research assistant who will assist in the screening, recruitment, scheduling and characterization of participants for the proposed study, as well as data management. Subject characterization will involve administering diagnostic interviews and neuropsychological tests. Data management will involve entering clinical data into a database under the supervision of the PI and assisting with fMRI data preprocessing. The salary of the research assistant will be incremented 3% per year in accordance with Research Foundation of Mental Hygiene, Inc. and Columbia University policies.

**SUPPLIES \$2,778**

1. Course Materials: \$500 is requested to course materials (e.g., textbooks) in year 1 ("Translational Bioinformatics", BINF G4006, Dept of Bioinformatics at CU; "Bayesian Statistics", W4640, Dept of Statistics at CU). Dr. Cha will audit these courses.
2. IT Supplies: \$2,000  
An external hard drive for storage (\$1,000) and a desktop computer (\$1,000) will be purchased for MRI data management and processing.
3. Office Supplies: \$278  
To cover general office supplies, printer cartridges, and poster printing costs for presentations.

**TRAVEL \$2,000**

1. Trip to NIMH (Dr. Pine's lab): Dr. Cha will travel to NIMH, Bethesda for one week to meet with Dr. Pine (advisor) to optimize the fear generalization task for fMRI and psychophysics, and the annual conference of Society of Biological Psychiatry to present the preliminary data and to meet with Dr. Pine.
- ❖ Trip to ETH Zurich (Dr. Stephan's lab): Dr. Cha will travel to Dr. Stephan's lab at ETH Zurich for two weeks to learn Hierarchical Bayesian Modeling. Dr. Cha will make this trip once per year throughout the course of this grant (i.e. four trips total). No travel costs for this trip are requested for Years 1 & 2, because the NARSAD Young Investigator award (see Biosketch—Cha) will support these travel costs. Travel costs are, however, requested for subsequent trips to ETH Zurich during Years 3 & 4 of this grant, after the NARSAD award ends.

**PUBLICATION COSTS \$3,000**

This cost is requested for all years to support publication fees at peer-reviewed journals such as figure costs and open access fees.

**OTHER EXPENSES \$23,060**

1. Scanning Costs: \$15,000
  - Dr. Cha will obtain scans on 75 participants from Year 1 to Year 3. Each scan will require 1 hour of time in the scanning suite at a cost of \$600 per hour.
  - Total cost for the duration of the study is \$46,363 (Year 1: \$600 x 25 scans = \$15,000; Year 2: \$618 x 25 scans = \$15,450; Year 3: \$636.54 x 25 scans = \$15,914). A 3% increase in Year 2-3 was applied as per Research Foundation of Mental Hygiene, Inc. and Columbia University policies.
2. Subject Fees & Transportation: \$3,000  
Subjects will be paid \$100 for their participation and \$20 for reimbursement for travel expenses (e.g., taxi). Total cost for the duration of the study (\$120 x 75 participants = \$9,000) will be divided equally in Year 1-3.
3. Software License Fee: \$560
  - \$200 is requested for license fee for data analysis software (e.g., MATLAB or SPSS).
  - \$360 (\$30 x 12 months) is requested for Citrix GoToMeeting® for monthly, quarterly meetings with off-site advisors (Drs. Pine, Klaas, Yoo).
4. Advertisement for Research Participant: \$1,500
  - Advertisement on local newspapers: \$2,500 = \$250/ad x 10 ads (in Year 1-3); we expect to recruit 20 participants (1 per ad) eligible for this study.
  - Online Advertisement (e.g., Google AdWords or Facebook): \$2,000 = \$1/cost per click x 2,000 clicks (in Year 1-3); we expect to recruit 20 participants (i.e., 1% of those who clicked the ad) eligible for the study.
  - Total cost of \$4,500 is equally split in Year 1-3.

## **COMPUTER AUTOMATED DATA PROCESSING SERVICES \$1,059**

1. PsyIT Services: \$1,059
  - NYSPI provides IT support for maintenance, upgrading, and troubleshooting for individual computers of \$730/FTE = \$1,059 for year 1, \$1,101 for year 2, \$1,145 for year 3, and \$1,191 for year 4.
  - These costs include a projected increase of 4% in continuing years as per Research Foundation of Mental Hygiene, Inc. and Columbia University policies.

## **YEARS 2 THROUGH 4**

The salary of the research assistant will be incremented 3% per year in accordance with Research Foundation of Mental Hygiene, Inc. and Columbia University policies. Other changes from the Year 1 budget include:

### **YEAR 2**

#### **PERSONNEL**

Research Assistant (6.1 Calendar Months effort)

#### **SUPPLIES \$1,653**

1. Course Materials: \$500 is requested to course materials (e.g., textbooks) in year 2 ("Development & Psychopathology", HUDK 5040, Dept of Psychology at CU; "Machine Learning for Data Science", W4721, Dept of Computer Science at CU). Dr. Cha will audit these courses.
2. IT Supplies: \$600  
Portable data storage device (\$600) will be purchased for MRI data management and processing.
3. Office Supplies: \$553

#### **TRAVEL \$2,000**

1. Anxiety and Depression Association of America (ADAA): Dr. Cha will travel to the annual conference to present the preliminary data and to meet Dr. Pine (advisor).
- ❖ Trip to ETH Zurich (Dr. Stephan's lab): This two-week trip is supported by the NARSAD award (ref. Year 1-Travel).

#### **PUBLICATION COSTS \$3,000**

#### **OTHER EXPENSES \$23,510**

1. Scanning Costs: \$15,450
2. Subject Fees & Transportation: \$3,000
3. Software License Fee: \$560
4. Advertisement for Research Participant: \$1,500

## **COMPUTER AUTOMATED DATA PROCESSING SERVICES \$1,101**

1. PsyIT Services: \$1,101

### **YEAR 3**

#### **PERSONNEL**

Research Assistant (5.45 Calendar Months effort)

#### **SUPPLIES \$878**

1. Course Materials: \$500 is requested to course materials (e.g., textbooks) in year 3 ("Risk, Resilience & Development Psychology", W4640, Dept. of Psychology). Dr. Cha will audit this course.
2. IT Supplies: \$200

3. Office Supplies: \$178

**TRAVEL \$4,000**

1. Computational Psychiatry Course: \$2,000 is requested. Dr. Cha will attend the Computational Psychiatry Course, organized by Dr. Stephan (an advisor) to learn cutting-edge computational modeling approaches in psychiatric research and neuroimaging.
2. Trip to ETH Zurich (Dr. Stephan's lab): In Year 3 & 4, \$2,000 is requested for this two-week trip (ref. Year 1-Travel).

**PUBLICATION COSTS \$3,000**

**OTHER EXPENSES \$19,474**

1. Scanning Costs: \$15,914
2. Subject Fees & Transportation: \$3,000
3. Software License Fee: \$560
4. Advertisement for Research Participant: \$1,500

**COMPUTER AUTOMATED DATA PROCESSING SERVICES \$1,145**

1. PsyIT Services: \$1,145

**YEAR 4**

**PERSONNEL**

Research Assistant (5.57 Calendar Months effort)

**SUPPLIES \$1,192**

1. IT Supplies: \$600
2. Office Supplies: \$592

**TRAVEL \$4,000**

1. American College of Neuropsychopharmacology (ACNP): In year 4, Dr. Cha will attend this annual conference to present the data and to meet an advisor, Dr. Pine.
2. Trip to ETH Zurich (Dr. Stephan's lab): In Year 3 & 4, \$2,000 is requested for this two-week trip (ref. Year 1-Travel).

**PUBLICATION COSTS \$3,000**

**OTHER EXPENSES \$19,560**

1. High Performance Computing system: \$19,000
  - High Performance Computing (HPC) system at Advanced Research Computing Services (ARCS) at CUMC
  - Data storage cost:  $\$7,600 = \$1,900 \text{ (per TB)} \times 4\text{TB}$
  - CPU usage cost:  $\$11,400 = (100,000 \text{ cpu hrs} \times 0.018 + 100,000 \text{ cpu hrs} \times 0.036) \times 8\text{GB}/3\text{GB}$  (memory surcharge)
  - CPU usage cost is requested to analyze multimodal MRI (structural, functional, diffusion MRI). The total estimate of CPU hours is based on a previous data analysis.
2. Software License Fee: \$560

**COMPUTER AUTOMATED DATA PROCESSING SERVICES \$1,191**

1. PsyIT Services: \$1,191

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	Totals (\$)
Section A, Senior/Key Person	486,000.00
Section B, Other Personnel	83,895.00
Total Number Other Personnel	4
Total Salary, Wages and Fringe Benefits (A+B)	569,895.00
Section C, Equipment	
Section D, Travel	12,000.00
1. Domestic	6,000.00
2. Foreign	6,000.00
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	104,101.00
1. Materials and Supplies	6,501.00
2. Publication Costs	12,000.00
3. Consultant Services	
4. ADP/Computer Services	23,496.00
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other 1	62,104.00
9. Other 2	
10. Other 3	
Section G, Direct Costs (A thru F)	685,996.00
Section H, Indirect Costs	54,880.00
Section I, Total Direct and Indirect Costs (G + H)	740,876.00
Section J, Fee	

## PHS 398 Cover Page Supplement

OMB Number: 0925-0001

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

Prefix: Dr.  
First Name\*: Jiook  
Middle Name:  
Last Name\*: Cha  
Suffix:

## 2. Human Subjects

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

## 3. 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

## 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)\*

.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

## PHS 398 Cover Page Supplement

### 5. 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://grants.nih.gov/stem\\_cells/registry/current.htm](http://grants.nih.gov/stem_cells/registry/current.htm). 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.

### 6. 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

### 7. 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\*:

## PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001

<b>Introduction (if applicable)</b> 1. Introduction to Application (for RESUBMISSION applications only)	
	FINAL_0314_1.pdf
<b>Candidate Information</b>	
2. Candidate's Background	FINAL1201_3.pdf
3. Career Goals and Objectives	FINAL1201_4.pdf
4. Career Development/Training Activities During Award Period	FINAL1452.pdf
5. Training in the Responsible Conduct of Research	FINAL1201_5.pdf
6. Candidate's Plan to Provide Mentoring (as applicable)	
<b>Statements of Support</b>	
7. Plans and Statements of Mentor and Co-Mentor(s)	FINAL1255.pdf
8. Letters of Support from Collaborators, Contributors, and Consultants	FINAL_10.pdf
<b>Environment and Institutional Commitment to Candidate</b>	
9. Description of Institutional Environment	FINAL1201_6.pdf
10. Institutional Commitment to Candidate's Research Career Development	FINAL_1424.pdf
<b>Research Plan</b>	
11. Specific Aims	FINAL1201_7.pdf
12. Research Strategy*	FINAL1201_8.pdf
13. Progress Report Publication List (for RENEWAL applications only)	
<b>Human Subject Sections</b>	
14. Protection of Human Subjects	working_0314_FINAL.pdf
15. Inclusion of Women and Minorities	FINAL1201_10.pdf
16. Inclusion of Children	FINAL1201_11.pdf
<b>Other Research Plan Sections</b>	
17. Vertebrate Animals	
18. Select Agent Research	
19. Consortium/Contractual Arrangements	
20. Resource Sharing Plan(s)	
<b>Appendix (if applicable)</b>	
21. Appendix	MANUSCRIPT IN PRESS.pdf
<b>Citizenship*:</b>	
U.S. Citizen or noncitizen national	
Non-U.S. Citizen with temporary U.S. visa	
<input checked="" type="checkbox"/> Permanent Resident of U.S. (If a permanent resident of the U.S., a notarized statement must be provided by the time of award)	
Permanent Resident of U.S. Pending	

## INTRODUCTION TO THE REVISED APPLICATION

We thank the reviewers for their thorough and constructive review as well as their enthusiasm for the previous application. They described that the training/career development plan as “well-organized,” the candidate and mentoring team are “stellar,” and the research project “innovative.” Our responses to critiques are summarized below.

	1 CAN.	2 CAR.	3 RES.	4 MEN.	5 ENV.
R1	2	1	2	1	1
R2	2	2	1	2	1
R3	2	3	3	2	1

Reviewers' critique scores of A0.

### 1. Concerns raised during discussion: "Minor concerns with sample size, comorbidity issues, and the wide age range with insufficient attention to developmental rather than just age factors"

**1) Age range:** The wide age range in the A0 may be central to the minor concerns above. Our initial rationale for using a wide age range (8-17 years old) was to collect pilot data for a future R01 study with the aim of charting developmental trajectories of fear generalization. Nevertheless, we agree that such a wide age range could significantly confound the main effect of interest, over-generalization of fear in anxious youth. Therefore, in this resubmission, we are restricting the *age range to 13-17 years old*, targeting postpubertal adolescents. **2) Feasibility of recruiting youth with a narrower age range:** The new, narrower, age range may be deemed to impede recruitment; however, our recruitment plan as detailed in the resubmission (see 12. Research Strategy—C2.3. Recruitment Procedures) presents feasibility of recruiting adolescents (ages of 13-17). We will recruit participants through word-of-mouth, advertisements in local media, referrals from medical professionals through various resources. These resources include research clinics: **(a) Pediatric Anxiety and Mood Research Clinic (PAMRC)** and **Children's Day Unit (CDU)** at CU/NYSPI, led by Dr. Rynn (advisor); **(b) CU Clinic for Anxiety and Related Disorders (CUCARD)** at CU/NYSPI, of which Dr. Rynn is the medical director, **(c) Children's Anxiety & Depression Clinic at Children's Hospital of New York at Presbyterian Medical Center (CHONY)**, of which Drs. Posner (mentor) and Rynn closely work with staff. Drs. Posner, Rynn, and Simpson (co-mentor) have long-standing relationships with these affiliated clinics, which see yearly more than 600 new adolescents (ages of 13-17) referred for anxiety disorders. This rich clinical research environment will facilitate recruitment. **3) Developmental factors:** In order to better characterize **developmental factors** on the fear generalization behavior and related brain measures for our exploratory aim, we will use *Tanner stages* in addition to age. On-site clinicians (e.g., Dr. Rynn) in the Children's Day Unit or Dr. Posner will perform Tanner stages. **4) Small sample sizes:** By restricting the age range to 13-17 years old, we are increasing sample size per age, thereby improving statistical power and decreasing developmental effects on the main measures (e.g., fear generalization behavior, vmPFC activation, and vmPFC connectivity). **5) Comorbidities:** We revised the exclusion criteria so that we now exclude “Current DSM-5 disorders other than an anxiety disorder.” Of note, we are maintaining trans-diagnostic sampling across anxiety disorders, because studies in adults show fear over-generalization across multiple anxiety disorders. We acknowledge that, because of this decision, this K01 study will not have adequate power to test neurobehavioral differences within different anxiety diagnoses. Nevertheless, the pilot data collected here will contribute to a future R01 study that can examine inter-diagnostic differences and commonalities.

### 2. Concerns raised by individual reviewers

**1) Varying sample sizes (R #1):** We thank the reviewer for pointing out this error, which we have corrected here. We will recruit youth with no anxiety (n=25), mild anxiety (n=25), and severe anxiety (n=25). **2) Same mentor (R #2):** Reviewer #2 noted that the same postdoctoral sponsor is serving as a K01 mentor. As we appreciated the importance of diverse, well-rounded training, we included a co-mentor, Dr. Simpson, with whom I recently started to work. We have also formed a multidisciplinary mentoring team with experts across several disciplines to ensure that I receive a diversity of training perspectives (see Career Development/Training Activities During Award Period). **3) Matching on age and gender (R #3):** We confirm that the 3 groups (i.e., youth with no anxiety, mild anxiety, and severe anxiety) will be matched on age, Tanner stage, gender, and handedness. **4) Protection of human subjects (R #3):** We will make every effort to ensure the safety of all participants (see Protection of Human Subjects). Dr. Posner (mentor) is a board certified child and adolescent psychiatrist and will be available to talk with participants and their families should any participant experience excessive distress or anxiety. The study will be conducted at an academic medical center with comprehensive child psychiatry clinical services. Appropriate referrals and emergency care is available and will be used if necessary. Study procedures including safety monitor have been approved by my institution’s IRB.

**3. Additional changes in A1—Candidate:** Since the initial submission, I received a NARSAD Young Investigator award; published 2 first-authored manuscripts in *J Neurosci* (accepted) and *Hippocampus*, 3 second-authored papers. I have 3 more first-authored manuscripts under review. In total, during the research training (MS, PhD, and postdoctoral), I have published 19 peer-reviewed articles (8 first-authored) and received 7 honors and awards.

## CANDIDATE'S BACKGROUND

I am committed to translational and developmental research focusing on the neural mechanisms of pathological anxiety. My prior training has focused on biological systems engineering, basic neurobiology, and human cognitive neuroimaging. This K01 award will enable me to pursue translational neuroscience to delineate the biological and cognitive bases of pathological anxiety in youth to improve diagnosis and treatment strategies.

**Undergraduate Training.** As an undergraduate at Korea University I studied ecological and environmental engineering in the College of Life Sciences. There I learned a holistic, systems approach to understanding complex biological systems such as ecological systems ranging from the microbial to forest level. In parallel, I was fascinated by human emotion, and deeply inspired by Dostoevsky's literature dissecting human psychology; I took additional courses on human emotion and cognition. These two experiences led me to decide to study how the human mind is engineered and to pursue a master's degree in neurobiology.

**Master's Training.** During my Master's training in neurobiology in the Department of Anatomy at Catholic Medical College in Korea, I studied the structural underpinnings of diverse gap junctions (i.e., electrical synapses), which are crucial for extensive coupling and swift intercellular signaling in retinal interneurons. Using neuroanatomical methodologies (e.g., immunohistochemistry and electron microscopy), I discovered stark morphological differences in gap junctions, explaining functional diversities of retinal interneurons<sup>11</sup>. I won a travel award to present those results at the Association for Research in Vision and Ophthalmology. My master's degree training equipped me with a neurobiologist's eye leading me to focus on the structure of the nervous system as an avenue to understanding its function.

**PhD Training.** I then moved with my wife and children from Korea to the US to pursue my PhD in Neuroscience at Stony Brook University. I conducted my thesis research and coursework in the Departments of Neurobiology and Biomedical Engineering. Under the mentorship of Dr. Lilianne Mujica-Parodi, I completed my dissertation, entitled "Neural underpinnings of anxiety: Multimodal magnetic resonance imaging approach." In adults with and without generalized anxiety disorder (GAD), I identified neural substrates of two constructs of the negative valence system—'acute threat (fear)' and 'potential threat (anxiety)'. This was my first scientific work with humans. I learned basic neuroimaging methodologies, cognitive tasks, and multivariate statistical modeling. Results of this research suggested corticolimbic correlates of maladaptive emotional processes in adults with GAD, such as fear generalization (published three first-authored papers). I also collaborated on studies of attentional bias in healthy adults (published two first-authored papers). I received two travel grants to present these findings at the Society for Neuroscience and Human Brain Mapping.

In addition to my thesis research, I assisted with a pediatric neuroimaging study (ages 4-6 years) in the same laboratory. This study used an affective task and functional near-infrared spectroscopy, and was designed to develop a neuroimaging marker of risk for developmental psychopathology. The study showed that network efficiency of toddlers' PFC during negative affect processing correlates with a child's capability for effortful control<sup>12</sup>. In this project, I helped to recruit toddlers and collect neuroimaging and eye tracking data. Here, I learned the importance of developmental neuroscience research in public mental health, and began to develop research skills in working with children. Based on this experience, I decided to pursue pediatric neuroimaging as a method for understanding psychopathology in youth.

**Postdoctoral Training.** I started my postdoctoral training under the mentorship of Jonathan Posner, MD in the Division of Child & Adolescent Psychiatry in the Department of Psychiatry at Columbia University Medical Center (CUMC) and the New York State Psychiatric Institute (NYSPI). I have been investigating abnormal brain connectivity that can reliably predict symptoms in youth with various psychiatric disorders, including ADHD and anorexia nervosa. During this training, I have been acquiring additional skills in the acquisition of multimodal MRI data in youth as well as large-scale data analysis using a super-computing system. I published a first-authored article about childhood ADHD reporting on the relationship between aggression and brain connectivity within the reward circuit in *Neuropsychopharmacology*<sup>13</sup>. This work resulted in an Outstanding Postdoctoral Researcher Award from the Association of Korean Neuroscientists at Society for Neuroscience. I recently published two first-authored papers in the *Journal of Neuroscience* (accepted) and *Hippocampus* reporting neural correlates of clinical anxiety in adults. Three more first-authored manuscripts are currently under review. These works resulted in two travel grants (Anxiety and Depression Association of America, and Wisconsin Symposium on Emotion), a Career Development Leadership Program award. I also recently received a NARSAD Young Investigator Award, which enables the initial hands-on training on a Bayesian modeling approach to fear generalization (in collaboration with Dr. Stephan, an advisor)—an area of expertise that I aim to further develop through this K01 Career Development plan so that I can employ these methods independently in my future research.

**Transition to Independent Career.** My ultimate career goal is to become an independent research scientist to develop brain measures predicting the development of pathological anxiety and guiding the development of novel treatment strategies. I will aim to elucidate threat processing behaviors and their underlying neural circuits across development and across the spectrum of anxiety from normal to pathological. My PhD training provided me with the opportunity to learn how to study anxiety in adults, the fundamentals of task-fMRI experimentation, and the analysis of diffusion MRI and resting state functional connectivity. In my postdoctoral training, I began understanding the fundamentals of pediatric neuroimaging research in children with ADHD. Now my goal is to successfully transition to research independence and compete for an R01-level longitudinal study to examine developmental trajectories of fear generalization. To achieve these goals, I need to develop the following: (i) **a sophisticated understanding of the phenomenology of anxiety disorders across the lifespan from children to young adults** (*Training Goal #1—phenomenology of anxiety disorders*), (ii) **expertise in translating developmental, affective neuroscience to patient-oriented research** (*Training Goal #2—patient-oriented, translational and developmental neuroscience of anxiety*), (iii) **competency in cutting-edge MRI data analysis strategies to improve both sensitivity and specificity of neuroimaging-based predictive modeling towards precision medicine** (*Training Goal #3—advanced computational neuroimaging*).

These additional experiences will help me to effectively link neuroscience and neuroimaging results to clinical populations, to facilitate developing neurobehavioral markers to promote a biologically-derived nosology of anxiety, and to develop neurobehavioral markers predictive of the development of psychopathology and treatment response. Lastly, as English is not my first language, my training will include mentorship to improve my skills in grant and manuscript writing as well as oral presentations. In sum, this K01 award will allow me to fully benefit from the didactics and hands-on mentored training essential for the attainment of my ultimate goal of becoming an innovative, NIH-funded, independent scientist.

## CAREER GOALS AND OBJECTIVES

My long-term career goal is to develop sensitive and specific neurobehavioral markers that can be ultimately used for early detection, intervention, and prevention of pathological anxiety in youth. Towards this end, my short-term goal is to learn the phenomenology of anxiety disorders, to acquire expertise in trans-diagnostic neuroimaging experimentation in youth with anxiety disorders, and to learn up-to-date imaging data analysis technologies. Since I have no formal training in these domains, to date, I have primarily relied on collaborators for my work. To enrich my skills and ensure my research independence, I have therefore developed three training objectives for the K01 award:

- (1) **Phenomenology of anxiety disorders from youth to young adults**
- (2) **Patient-oriented, translational and developmental neuroscience of anxiety**
- (3) **Advanced computational neuroimaging.**

Newly developed skills and expertise in these three areas along with the data from the proposed study described below will lead to a successful R01-level proposal, a longitudinal study across the developmental stages, from children to young adults with the goal of delineating developmental trajectories of fear generalization and pathological anxiety. This future study will aim to identify behavioral and neuroimaging biomarkers that predict developmental changes of fear processing behavior and of brain circuits, and thus facilitate early detection of and interventions of pathological anxiety.

## CAREER DEVELOPMENT/TRAINING ACTIVITIES DURING AWARD PERIOD

During this K01 Award, I will focus on three areas essential to successful transition to research independence and responsible conduct of research. The mentoring team consists of experienced, leading scientists in anxiety disorders across the lifespan, translational and developmental neuroscience, and computational data analysis. Through this mentoring team, this K01 award will enable me to develop productive collaborations with leading researchers worldwide, which will contribute to my independent research career. The training plan will be implemented and overseen by two mentors, Drs. Jonathan Posner and Helen Blair Simpson, with weekly meetings throughout the K01 period to ensure that timely progress is made towards (1) publication of research articles for each training/research aim, and (2) preparation of an R01 application to NIH. Drs. Posner and Simpson will organize a quarterly meeting with the other advisors using web conferencing to review progress, to identify any roadblocks to success, and to ensure that training and research goals are being met.

**Mentoring Team.** **Dr. Jonathan Posner** (*primary mentor*) is a clinician-researcher in child psychiatry and pediatric neuroimaging. His research focuses on the use of MRI to understand the neural bases of emotional processing and regulation in a range of psychiatric disorders affecting children. He has been a principal investigator on several NIH grants including NIMH K23, R01, and R21 awards, and is the project leader for a Multimodal Imaging Core within a Conte Center examining the effects of serotonergic modulation on brain development. I have established a successful track record of research with Dr. Posner (2 publications<sup>13, 14</sup>; 3 in review). Dr. Posner is an ideal choice as primary mentor in this application because his expertise in developmental neuroimaging is central to the proposed research.

**Dr. Helen B. Simpson** (*co-mentor*) is an authority on translational research in psychiatry to transform the current diagnosis and treatments for anxiety, obsessive-compulsive disorder (OCD), and related disorders. She uses clinical trial methodology to test new treatments in patients with anxiety disorders and to determine how to combine and sequence current treatments to maximize outcome. Dr. Simpson participates in the RDoC initiative at the NIMH, first as a member of the Negative Valence Systems Workshop, and now as the Principal Investigator of an NIMH-grant (R01) consistent with the RDoC approach. Dr. Simpson also was awarded a NIMH midcareer investigator award in patient-oriented research (K24), recognizing her commitment to mentoring and training in patient-oriented research in OCD and related anxiety disorders. Drs. Simpson, Posner, and I have recently published an article together<sup>14</sup>. Dr. Simpson is an ideal mentor for this proposal because of her clinical experiences in adulthood anxiety disorders, her track record of patient-oriented and translational research, and her experience of successful mentoring towards research independence.

**Dr. Moira Rynn** (advisor #1) is Chief of the Division of Child & Adolescent Psychiatry at Columbia University/New York State Psychiatric Institute (CU/NYSPI). Her research is focused on psychopharmacological studies of pediatric anxiety disorders. Dr. Rynn is the co-principal investigator on the Child Child/Adolescent Anxiety Multimodal Treatment Study (CAMS<sup>15</sup>). Dr. Rynn is an ideal advisor for Training Goal #1 because of her expertise in the phenomenology, treatment, and characterization of pediatric anxiety disorders.

**Dr. Daniel S. Pine** (advisor #2) is Chief of the Section of Development and Affective Neuroscience at NIMH. His research is focused on translational neuroscience including biological aspects of anxiety in humans across the lifespan. Dr. Pine is an ideal advisor for Training Goal #2 because of his leading role in applying affective neuroscience, psychophysiological and neuroimaging experimentation to studies of pediatric anxiety.

**Dr. DuBois Bowman** (advisor #3) is Chair of the Department of Biostatistics at CU/NYSPI, whose research is focused on the development of predictive modeling for biomarkers of depression, schizophrenia, and cocaine addiction by integrating multimodal (e.g., functional and diffusion) MRI. Dr. Bowman is an ideal advisor for Training Goal #3 because of his expertise in advanced statistical modeling of neuroimaging.

**Dr. Klaas E. Stephan** (advisor #4) is Director of the Translational Neuromodeling Unit at ETH Zurich, whose research is focused on development of computational tools delineating maladaptive emotional processes using neuroimaging. He is an ideal advisor for Training Goal #3 because of his expertise in Bayesian modeling to infer mechanisms of brain disease from neurobehavioral measures.

**Dr. Shinjae Yoo** (advisor #5) is a data scientist at Brookhaven National Laboratory, who has developed state-of-the-art machine learning algorithms in data-intensive fields, such as nuclear physics and climate science. He is an ideal advisor for Training Goal #3 because of his expertise in big data science.

### Goal 1: Phenomenology of anxiety disorders from youth to young adults

**Rationale.** I seek to acquire proficiency in the etiology, phenomenology, and assessments of pathological anxiety across the lifespan from children to young adults. Given my research focus on youth with pathological anxiety, I need to be fluent not only in formal diagnoses, but across the spectrum of disorders and symptomatology of childhood anxiety disorders. This training is an essential prerequisite for me to become a fully

independent investigator conducting translational research in anxiety disorders. **Drs. Simpson and Rynn** will supervise my training in this area.

#### **Coursework.**

1. Anxiety Disorders (young adults): Directed by **Dr. Simpson**, this is a 10-session course in the psychiatry residency program at CU, covering the phenomenology and psychobiology of anxiety disorders.
2. Psychopathology (children and adolescents): Directed by **Dr. Laurence Greenhill**, a course in the child and adolescent psychiatry residency program at CUMC. Recommended by Dr. Rynn, this will cover clinical assessments and diagnosis of anxiety disorders and offer firsthand experiences with patients.

#### **Supervision and Hands-On Practicum.**

1. Anxiety Disorders in Young Adults: I will meet with **Dr. Simpson** weekly at CU/NYSPI to learn to screen a range of anxiety disorders and relevant clinical measures in young adults.
2. Anxiety Disorders in Children and Adolescents: (1) I will attend weekly Friday research meetings in the Children's Day Unit (CDU) directed by Dr. Rynn to learn about clinical cases, therapeutics, and clinical research. (2) I will also meet one-on-one with Dr. **Rynn** monthly at CU/NYSPI to review the progress of the training and observership of clinical assessments, psychotherapy, and research at CDU.

#### **Goal 2: Patient-oriented, translational, developmental neuroscience to anxiety disorders**

**Rationale.** I seek to acquire expertise in translating developmental neuroscience research to patient-oriented research in anxiety disorders. This is crucial to harness basic neuroscience knowledge, and the neuroimaging approach to achieve better understanding, treatment, and prevention of anxiety disorders. Successful completion of this training goal will help me design and conduct neuroscience studies using a dimensional, not categorical, approach and a transdiagnostic approach, and translate the research outcomes to inform diagnosis and treatment of anxiety disorders. **Drs. Posner, Simpson, and Pine** will supervise this training.

#### **Coursework.**

1. Development and Psychopathology (HUDK 5040, Dept. of Psychology at CU) will focus on the interface between classical developmental psychology theories and atypical development patterns.
2. Risk, Resilience and Development Psychology (HUDK 6529, Psychology Dept. at CU) will cover developmental models for understanding risk and resilience.

#### **Supervision and Hands-On Practicum.**

1. Translational Pediatric Neuroimaging (1) I will meet with **Dr. Posner** weekly at CU/NYSPI to discuss study design, recruitment, MRI data collection in youth with or without anxiety disorders. (2) I will attend a weekly meeting of Dr. Posner's lab at CU/NYSPI to learn about translational neuroimaging study in youth.
2. Translational Neuroscience to Clinical Anxiety: (1) I will meet with **Dr. Simpson** weekly at CU/NYSPI to discuss how to identify neurocognitive and neuroimaging biomarkers for pathological anxiety, and based on the identified measures, how to establish a new way to classify pathological anxiety; (2) I will attend the weekly science meeting at the Anxiety Disorders Clinic, led by **Dr. Simpson**, where experts in patient-oriented, translational research in anxiety-related disorders present ongoing research.
3. Translational, Affective, Developmental Neuroscience: I will meet with **Dr. Pine** monthly via conference call to discuss how to use insights from neuroscience to inform understandings of risk, diagnosis, and treatment of anxiety disorders. I will also visit **Dr. Pine**'s lab at NIMH to learn psychophysiological and functional neuroimaging experiments in youth with anxiety disorders (1wk/yr) in Year 1.

**Seminars and Conferences.** I will attend Columbia Translational Neuroscience Initiative (CTNI) Symposium (CTNI represents disease-focused neuroscience research centers at CUMC to enhance basic and translational neuroscience research). I will also attend the annual meetings of the Biological Psychiatry, American College of Neuropsychopharmacology (ACNP), Anxiety & Depression Association of America (ADAA) to present the K01 research and to meet with **Dr. Pine**.

#### **Goal 3: Advanced computational neuroimaging**

**Rationale.** My long-term goal is the development of neuroimaging measurements with sufficient sensitivity and specificity for diagnosis of mental disorders, which requires robust computational methods. I have previously used structural equation modeling and multivariate analyses in neuroimaging studies, but these were not originally designed for single-subject level prediction. Thus, I seek additional training in cutting-edge computational methods including predictive modeling, integrating structural and functional connectivity, model-based fMRI analysis, state-of-the-art big data science approaches that have been successfully applied to computation-intensive fields, but are yet to be applied to neuroimaging (e.g., social network analysis, physics, bioinformatics and climate science). **Dr. Bowman** will supervise this training goal and **Drs. Stephan and Yoo** will provide additional consultation.

**Table 1. K01 Training Aims and Activities.**

Formal Didactic Course		Seminars & Conferences		Tutorials & Hands-on Practicum	
Training Aim	Year 1	Year 2	Year 3	Year 4	
<b>1. Phenomenology of anxiety disorders</b>	<ul style="list-style-type: none"> <li>Anxiety Disorders (2hr/wk; fall)</li> <li>Psychopathology (2hr/wk; spring)</li> </ul>				
	<ul style="list-style-type: none"> <li>Anxiety Disorders in Young Adults: <b>Dr. Simpson</b> (one-on-one meeting–1hr/wk)</li> <li>Anxiety Disorders in Children and Adolescents: <b>Dr. Rynn</b> (research meeting in Children's Day Unit (CDU)–1hr/wk; 1-on-1 meeting–1hr/mo)</li> </ul>				
<b>2. Patient-oriented, translational, neuroscience to anxiety disorders</b>	• Development and Psycho-Pathology (4hr/wk; summer)	• Risk, Resilience & Development psychology (1hr/wk; fall)			
	<ul style="list-style-type: none"> <li>Columbia Translational Neuroscience Initiative (CTNI) symposium (1hr/wk)</li> <li>Society of Biological Psychiatry (4d/yr)</li> <li>ADAA (3d/yr)</li> </ul>		<ul style="list-style-type: none"> <li>ACNP (5d/yr)</li> </ul>		
	<ul style="list-style-type: none"> <li>Translational Pediatric Neuroimaging: <b>Dr. Posner</b> (research meeting in Laboratory for Pediatric Neuroimaging–1hr/wk; 1-on-1 meeting–1hr/wk)</li> <li>Patient-oriented, Translational Neuroscience: <b>Dr. Simpson</b> (Anxiety Disorders Clinic science meeting–1hr/wk; 1-on-1 meeting–1hr/wk)</li> <li>Translational, Affective, Developmental Neuroscience: <b>Dr. Pine</b> (meeting via conference call–1hr/mo; visit Dr. Pine's lab to learn psychobiology experiments in 1w/yr in Year 1)</li> </ul>				
	<ul style="list-style-type: none"> <li>Translational Bioinformatics (4hr/wk; fall)</li> <li>Bayesian Statistics (4hr/wk; spring)</li> </ul>	<ul style="list-style-type: none"> <li>Machine Learning for Data Science (4hr/wk; spring)</li> </ul>			
<b>3. Advanced computational neuroimaging</b>	<ul style="list-style-type: none"> <li>Data Science Institute Colloquium (1hr/wk)</li> <li>Biostatistics Seminar (1hr/wk)</li> <li>Data Science Institute Bi-annual symposium (2d/yr)</li> </ul>		<ul style="list-style-type: none"> <li>Computational Psychiatry Course (3d/yr; Switzerland; Dr. Stephan)</li> </ul>		
	<ul style="list-style-type: none"> <li>Integration of Multi-Modal MRI for Biomarkers of Anxiety: <b>Dr. Bowman</b> (1-on-1 meeting–1hr/mo)</li> <li>Advanced Bayesian Modeling: <b>Dr. Stephan</b> (training at the Translational Modeling Unit–2wk/yr in Year 1-4; meeting via conference call–1hr/mo)</li> <li>Big-data science approach to neuroimaging: <b>Dr. Yoo</b> (1-on-1 meeting–1hr/mo)</li> </ul>				
<b>Career development for independence.</b>	<ul style="list-style-type: none"> <li>Writing a Successful NIH Grant Application (1hr/wk; summer)</li> </ul>		<ul style="list-style-type: none"> <li>Funding for Research (1hr/wk; summer)</li> </ul>		
<b>Ethics: Responsible Conduct of Research</b>	<ul style="list-style-type: none"> <li>Responsible Conduct of Research (1hr/wk; spring)</li> <li>Annual Ethnics Symposium (1hr/wk)</li> <li>Psychiatric Ethics (1hr/wk)</li> </ul>				
	<ul style="list-style-type: none"> <li>1-on-1 meetings with <b>Drs. Posner</b> (advisor; 1hr/wk), <b>Simpson</b> (co-mentor; 1hr/wk), <b>Rynn</b> (advisor; 1hr/mo)</li> </ul>				

**Coursework.**

1. Translational Bioinformatics (BINF G4006, Dept of Bioinformatics at CU): Recommended by Dr. **Bowman**, this will cover core methods in biomedical data science, such as statistical and computational algorithms to evaluate large biomedical data (e.g., graph theoretic models and network analysis).
2. Bayesian Statistics (W4640, Dept. of Statistics at CU) will provide a foundation of Bayesian inferences and modeling including Bayesian hierarchical models. As suggested by Dr. **Stephan** (advisor), the theoretical knowledge acquired from this course will help me apply hierarchical Bayesian models to fear generalization data in the research plan.
3. Machine Learning for Data Science (W4721, Dept. of Computer Science at CU): Recommended by Dr. **Yoo**, this will provide an introduction to the field of machine learning and hands-on experience in the application to various data, including fMRI time series or MR-based connectivity data.

**Supervision and Hands-On Practicum.**

1. Integration of Multimodal MRI for Biomarkers of Anxiety: I will meet with Dr. **Bowman** monthly at CU/NYSPI to discuss advanced statistical methods for integration of structural and functional connectivity measures. This knowledge will be used in Specific Aim #1 & #2.
2. Advanced Bayesian Modeling: I will visit Dr. **Stephan**'s lab (Translational Neuromodeling Unit) at ETH Zurich in Zurich, Switzerland to learn how to use Bayesian models (e.g., Hierarchical Gaussian Filtering) to infer mechanisms of brain disease from neurobehavioral measures in each year of the K01 period for two weeks (2w/yr). These models aim to quantify physiological and computational principles (e.g., reinforcement learning) underlying maladaptive cognition, such as fear over-generalization. Building on the connection with Dr. Stephan initiated by the NARSAD award (see Biosketch—Cha), this and the other training activities (e.g., Bayesian Statistics course and the Computational Psychiatry Course), and the new K01 research data that I will analyze using these methods (see 12. Research Strategy—C2.11. Bayesian Learning Modeling) will help me become an expert in the Bayesian modeling approach to fear generalization. Also, I will meet with Dr. **Stephan** monthly via conference call to discuss analyzing the K01 research data.
3. Big-Data Science Approach to Neuroimaging and Psychiatric Research: I will meet with Dr. **Yoo** monthly at Stony Brook University (1.5hr drive from CU) or via Google video chat to discuss big-data science approaches (e.g., data mining techniques and scalable computational methods).

**Seminars and Conferences.** I will attend the Computational Psychiatry Course (Switzerland, 3d/y), organized by Dr. Stephan, to learn computational model-based approaches to psychiatric research; Data Science Institute Colloquium (Data Science Institute, CU; 1hr/w), Data Science Institute Biannual symposium (2d/yr), and Biostatistics Seminar (CU/NYSPI; 1hr/wk).

## TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH

### Rationale.

Ethical conduct is the crucial prerequisite for biomedical research, particularly when involving vulnerable populations such as anxious children and adolescents. In my former PhD training in the Department of Neurobiology and Behavior and the Department of Biomedical Engineering in the School of Medicine at Stony Brook University, I had extensive training in the responsible conduct of research. I will continue this training throughout the award period through didactic courses, seminars, and one-on-one meetings with mentors at Columbia University Medical Center and the New York State Psychiatric Institute (CU/NYSPI).

### Previous Training.

- |                                    |   |
|------------------------------------|---|
| 1. PhD at Stony Brook University   | • <b>Ethical Research</b> at Stony Brook University (directed by Dr. David Talmage, Associate Professor in the Department of Pharmacological Sciences, 1hr/wk). This course covered data collection and management, attribution of credit, plagiarism, peer review, and conflicts of interest.  |
| 2. Postdoctoral Fellow at CU/NYSPI | •Online courses required by CUMC through Research Compliance and Administration System. This training was specifically designed for researchers working with human subjects. Topics included: Information Security, Privacy & HIPAA (Health Insurance Portability and Accountability Act), Human Subjects Protection and Good Clinical Practices. |

### Plan for Training.

- |                       |  |
|-----------------------|--|
| 1. Course             | • <b>Responsible Conduct of Research and Related Policy Issues</b> at CUMC (directed by Dr. Richard Kessin, Professor in the Department of Pathology and Cell Biology; G4010, 1hr/wk). This course explores ethical and policy issues during the conduct of basic, translational, and clinical biomedical scientific research. Specific topics include: research misconduct, human research participants and scientific research, data sharing and data secrecy.   |
| 2. Seminar            | • <b>Seminar in Applied Psychiatric Ethics</b> at CUMC ( <i>Columbia Psychiatry Residency Program</i> , directed by Drs. David Lowenthal, Clinical Director, and David Strauss, Director of Psychiatric Research and Vice Chairman for Research Administration, Ethics and Policy). This course covers concepts in psychiatric ethics, such as sexual misconduct with patients and colleagues, research ethics, and ethical problems in various clinical circumstances.<br><br>• <b>Annual Ethics Symposium</b> at NYSPI (directed by Dr. Ilene F. Wilets, the Chair of the NYSPI-IRB). This is a day-long workshop that addresses special issues concerning the capacity to consent to research and guardianship. |
| 3. One-on-one meeting | • <b>Weekly Meetings with Drs. Posner (mentor) and Simpson (co-mentor)</b> . We will discuss practical issues in the ethical treatment of youth, particularly those with clinical anxiety disorders, and research conduct in our weekly one-on-one meetings.<br><br>• <b>Monthly Meetings with Dr. Rynn</b> at NYSPI ( <b>advisor</b> , Chair of the Division of Child and Adolescent Psychiatry and Director of Pediatric Anxiety and Mood Research Clinic). We will also discuss issues of informed consent, evaluation and responsible practices with regard to assessment and monitoring of children and adolescents with anxiety disorders.   |

## Research Foundation for Mental Hygiene, Inc.

New York Psychiatric Institute Division  
1051 Riverside Drive • New York, New York 10032  
(646) 774-6500 • (646) 774-6540

February 2, 2016

Dear Colleagues:

I whole-heartedly and unequivocally support Dr. Jiook Cha's application for Mentored Research Scientist Career Development (K01) Award entitled, "*Neural Correlates of Fear Over-Generalization in Youth with Pathological Anxiety*". I recruited Dr. Cha to come to Columbia after completing his PhD at Stony Brook University, and have had the distinct pleasure of working closely with him since then. Dr. Cha is an investigator of exceptional intelligence, determination, persistence, and intellectual curiosity, who has a steadfast commitment to advance our understanding of the neural mechanisms of psychiatric disorders. He has demonstrated unprecedented facility with inter-disciplinary methodologies imperative to successfully meeting the challenges of a career path in the neuroimaging of anxiety disorders in children and adolescents. Dr. Cha is extremely adaptable in seeking innovation and ardent in the pursuit of his academic and career goals. During his doctoral and postdoctoral trainings, he has demonstrated the ability to lead independent projects and tackle crucial questions in affective neuroscience and psychiatry. I have no doubt that Dr. Cha will become a leading investigator in neuroimaging research in pediatric anxiety research, and I assure that I am fully committed to supporting his research career.

Dr. Cha joined my lab after completing his PhD training in the Department of Neurobiology and Behavior at Stony Brook University. As his postdoctoral advisor, I work closely with Dr. Cha and have firsthand experience of his innovative research, strong work ethic, and valuable contributions to the field. Dr. Cha's unique academic background thus far has led him to take an innovative approach to psychiatry. Dr. Cha obtained his Bachelor of Science in Environmental Engineering at Korea University in Korea and his Master's degree in Neurobiology studying basic neurobiology in the Catholic University of Korea. Dr. Cha then completed his PhD in Neuroscience at Stony Brook University, New York. For his thesis research, entitled, "*Neural underpinnings of anxiety: Multimodal magnetic resonance imaging approach*," he brought his interests in integrative approach into human cognitive and affective neuroimaging research. In his four first-authored articles published in the *Journal of Neuroscience*, *Cerebral Cortex*, and *Cortex*, he reported mesocorticolimbic substrates of anxious behaviors in clinical and non-clinical individuals using an elegant methodology combining structural, functional, and diffusion MRI and connectivity mapping, and behavioral paradigms (e.g., fear generalization and negative attention bias). These are an exceptional series of studies bridging affective neuroscience, cutting-edge neuroimaging, and clinically oriented research.

I was delighted when Dr. Cha decided to pursue patient-oriented, translational neuroscience research in child psychiatry. Child psychiatric research needs talented and dedicated young investigators like Dr. Cha. I believe that his innovative approach to research and his drive for studying the neural underpinnings of anxiety disorders in youth will have a significant impact on the field. During his fellowship, Dr. Cha aimed to study brain correlates of childhood mental illnesses applying his neuroimaging expertise. During the two-year fellowship, Dr. Cha published 3 first-authored articles in *Neuropsychopharmacology*, *Hippocampus*, and the *Journal of Neuroscience*: the first reports structural connectivity (diffusion tractography) within the corticostriatal reward circuit that predicts aggression in children with ADHD; the second reports abnormal hippocampal structure and threat-processing function in anxiety and comorbid depression; and the last reports disrupted feedback connections in clinical anxiety. Dr. Cha also published 3 second-authored articles in *Neuropsychopharmacology* (two) and *Brain Structure and Function*, and wrote 3 first-authored manuscripts that are currently in review.

This excellence in research has led Dr. Cha to win a prestigious NARSAD Young Investigator Award in July 2015. This award funds his innovative computational modeling approach to infer on neuromodulatory mechanisms (e.g., prediction error of threat) underlying fear generalization in youths. Dr. Cha also received a travel grant award and a Career Development Leadership Program at the Anxiety and Depression Association of America (ADAA) conference in 2015. These remarkable achievements within a short period of time clearly indicate the quality of Dr. Cha's research and its impact on the field of psychiatric research, as well as the fruitful synergism of the mentoring program.

To become a successful, independent researcher at the interface of translational neuroscience and psychiatric research, Dr. Cha has so far proven to possess extraordinary commands of methodologies in neuroimaging

and affective neuroscience. His ambition is to use a longitudinal approach to chart the development course of fear generalization and over-generalization in healthy and pathologically anxious youth, respectively. Ultimately, Dr. Cha aims to use this research to fuel the development of novel prevention strategies and treatments for pathological anxiety. This Mentored Career Development award is an ideal way to launch this important line of research by first examining fear generalization in youth using a cross-sectional design. His training goals will solidify his knowledge of: (1) **psychopathology and clinical assessments of childhood and adulthood anxiety disorders**, (2) **patient-oriented, translational, developmental neuroscience in youth with pathological anxiety**, (3) **advanced computational methods in neuroimaging**, and (4) responsible conduct of research. Under each goal, we have designed well-balanced programs consisting of formal didactic coursework, supervision and hands-on practicum, as well as seminars and conferences. For example, the formal didactic courses are: for Training Goal #1, Anxiety Disorders and Psychopathology in the CU Psychiatry Residency Program, directed by Dr. Simpson, co-mentor; for Training Goal #2, Development and Psychology and Risk, Resilience and Development Psychology (the Dept of Psychology at CU); for Training Goal #3, Translational Bioinformatics (the Dept of Bioinformatics at CU), Machine Learning for Data Science (the Department of Computer Science) and Bayesian Statistics (the Dept of Statistics at CU).

I will supervise and ensure the overall progress of Dr. Cha Career Development Award. I will provide training in pediatric neuroimaging and developmental neuroscience in our weekly one-on-one meetings. I will oversee the coordination and completion of each specific goal of the training plan together with the co-mentor Dr. Simpson in our monthly meeting. I am also committed to providing training in the Responsible Conduct of Research. Dr. Cha will attend a formal course provided by CU/NYSPI in Year 1 of the award, with additional training specific to his research project in our weekly and monthly (with Dr. Simpson) meetings.

We designed Dr Cha's training plan to provide an outstanding mentoring team with complementary expertise: **Dr. Helen B. Simpson** (co-mentor; Director of Anxiety Disorder Clinic at CU/NYSPI), as well as advisors consisting of seasoned scientists with complementary expertise: **Dr. Moira Rynn** (advisor #1; Chief of the Division of Child and Adolescent Psychiatry at CU/NYSPI), **Dr. Daniel Pine** (advisor #2; Chief of the Section on Development and Affective Neuroscience at NIMH), and **Dr. Dubois Bowman** (advisor #4; Chair of the Biostatistics Department at CU/NYSPI). I have existing established collaborative relationships with these colleagues. Two additional advisors include **Drs. Stephan Klass** (advisor #5; Director of Translational Neuromodeling Unit at ETH Zurich and University of Zurich) and **Shin-Jae Yoo** (advisor #6; Associate Computational Scientist at Brookhaven National Laboratory). Dr. Klass and I are currently collaborating on the computational approach to study impulsivity in youth ADHD. Each member of the mentoring team will supervise complementary components of the training as described in Dr. Cha's training proposal. With this mentoring team and the excellent resources available at CUMC and NYSPI, Dr. Cha is ideally positioned for this Mentored Research Scientist Development (K01) award.

Dr. Simpson (co-mentor) and I, together with the advisors, will convene quarterly meetings to review overall progress of the research and training. I will also provide Dr. Cha with annual written feedback that represents his progress towards his training, research and academic goals, which we will also discuss in person.

My qualifications and mentoring experience make me well suited for the role of primary mentor on Dr. Cha's application. I have extensive expertise in using multimodal MRI to study a range of disorders in youth. I have published more than 25 peer-reviewed scientific articles. I am the associate training director for research training in the Division of Child and Adolescent Psychiatry at CUMC and have significant experience as a supervisor and mentor. I have been a principal investigator on 3 NIH grants including NIMH-funded K23, R01, and R21 awards, and I am the Director of a Neuroimaging Core within a Conte Center examining the effects of serotonergic modulation on brain development. I also have extensive experience working with Dr. Helen B. Simpson (co-mentor). We are currently collaborating on two NIH funded studies, and have published together previously.

Over the period of this K01 award, several publications are expected. First, towards the end of Year 1, Dr. Cha will analyze the data under Aim #1, "investigating fear generalization effects and the underlying corticolimbic circuit in healthy youths". We expect to write at least one peer-reviewed article from this analysis—**publication #1**. Considering the paucity of literature on the neural underpinnings of the fear generalization, the expected paper will be a significant contribution to the field. Second, towards the end of the Year 3, Dr. Cha will be able to analyze that data under Aim #2, "investigating excessive fear generalization in youths with pathological anxiety". We expect to write a second paper using this data—**publication #2**. Third, towards Year 4, once Dr. Cha completes the training in advanced computational methods, he will apply the knowledge to the data under

both Aims. We expect at least two papers from this. One will be about charting maturation of the corticolimbic system associated with fear generalization through integration of structural and functional connectivity (using Bayesian statistics framework)—**publication #3**. The other one is feasibility of predictive modeling of brain states associated with fear generalization and pathological anxiety using multiple units of analysis—**publication #4**. Given Dr. Cha's track record of publication (7 first-authored publications in the prior academic training), this is a very reasonable expectation. Of note, all aspects of the proposed research project will constitute Dr. Cha's own research program.

Another essential component of this training plan is to provide effective training for Dr. Cha to successfully compete for research grants. Completing for research grants is crucial to transitioning to an independent, research career. I will mentor Dr. Cha on applying and successfully competing for various research grants at CUMC and independent foundations. Dr. Cha and I have identified several pilot research grants, which fit well with the specific research and training aims of his proposal. (1) International Short Visit Fellowship Program (Swiss National Science Foundation; Goal 3-Computational Psychiatry); (2) Clinical and Translational Research Grant (CUMC; Goal #2-Translational Neuroscience); (3) Research Opportunities and Approaches to Data Science (Data Science Institute, CU; Goal #3-Computational Psychiatry).

Drs. Cha, Simpson and I designed this training plan to maximize Dr. Cha's research related career development. During the award phase, therefore, Dr. Cha will not be required to teach, serve on committees, or hold any administrative assignments.

Lastly, we have designed a plan to ensure successful transition from a mentored to an independent investigator. I will enthusiastically assist Dr. Cha in his search for a University-based tenure-track position both by providing suggestions for jobs openings and reaching out through my network of colleagues. I will review Dr. Cha's drafts of research statements, and cover letters when he applies for independent positions towards the later phase of the award period. I will also assist Dr. Cha in preparing his job talks, interviews, and job negotiation.

In conclusion, Dr. Cha is an exceptionally talented young scientist and we are fully committed to advancing his career. He is an ideal candidate for a Mentored Research Scientist Career Development (K01) Award – talented, dedicated, ambitious, intelligent, and creative – and we have no doubt that he will make important scientific contributions. NIH cannot go wrong in investing in such an outstanding candidate.

Sincerely,

Jonathan Posner, MD  
Associate Professor of Clinical Psychiatry  
Columbia University Medical Center  
The New York State Psychiatric Institute

## Research Foundation for Mental Hygiene, Inc.

New York Psychiatric Institute Division

1051 Riverside Drive • New York, New York 10032

(646) 774-6500 • (646) 774-6540

February 11, 2016

Dear Colleagues:

I am writing this letter with great enthusiasm for Dr. Jiook Cha as he applies for a K01 Mentored Career Development award. Born in Korea with a PhD from Stony Brook University in Neuroscience, Dr. Cha is an extraordinary young scientist who seeks to understand the brain mechanisms underlying pathological anxiety in youth. Ambitious, creative, and very hard working, Dr. Cha has the right stuff to become a future leader in our field. This K01 application will give him the necessary skills and preliminary data to launch an independent research career in translational psychiatry.

Jiook's proposal aims to investigate fear generalization and the underlying corticolimbic circuit in youths with anxiety disorder and in healthy controls. Normative fear generalization is an important adaptive learning mechanism, and excessive fear generalization is one potential process that leads to pathological anxiety. This will be the first fear generalization neuroimaging study in youths. By combining fMRI task, behavioral measures, and multimodal neuroimaging, Jiook's proposal embodies the interdisciplinary approach aiming at delineating neurobehavioral mechanisms of clinical anxiety with multiple units of analysis. His proposal employs a sophisticated approach, which he has previously, successfully applied to adults with Generalized Anxiety Disorder in his PhD training.

Closely linked to this research plan, Jiook's training plan is designed to enable him to successfully transition to research independence. He has four main training goals: 1) to learn about the clinical phenomenology of pathological anxiety in both youth and adults; 2) to learn how to conduct patient-oriented translational research, bridging the gap between neuroscience and psychiatry; 3) to learn advanced computational methods in neuroimaging; and 4) responsible conduct of research. This training will equip Jiook with knowledge and expertise critical not only for successful completion of the research plan, but also for his ambition towards developing neuroimaging-based precision medicine in psychiatry.

I am excited to serve as his co-mentor along with my collaborator Dr. Jonathan Posner. As co-mentor, I will help Dr. Posner supervise Jiook's overall progress of research and training, with Dr. Posner supervising the neuroimaging progress and my supervising the clinical research piece. I will also specifically help Jiook with two of his training goals as outlined in his training plan. Specifically, I will help to train Jiook in the phenomenology of anxiety disorders through our weekly meetings and didactic course that I teach in the Psychiatry Residency program, Anxiety Disorders, at New York Presbyterian Hospital-CU/NYSPI. I will also help to train Jiook in how to conduct patient-oriented translational research through our individual meetings and his joining the weekly scientific meetings of the research clinic that I direct, where we discuss patient-oriented translational studies in anxiety disorders. Finally, I will organize a quarterly meeting, together with Dr. Posner (primary mentor) and other members of the mentoring team to review his scientific and career progress; we will ensure that he completes his training goals, develops data that can lead to a successful R01 application, and develops superior skills in oral and written presentations that will be critical for his success.

I am well-suited to serve as Jiook's co-mentor. I have been continuously funded by NIMH since 1999 to pursue patient-oriented translational research in patients with anxiety disorders. Throughout my career, I have mentored numerous junior faculty and students in career development awards at the post-doctoral, and doctoral levels. My post-doctoral and junior faculty mentees have gone on to assume productive faculty positions at major research institutes. As a result, I know the skills that young scientists need to develop to become independent researchers. In recognition of my mentoring abilities, I was awarded a NIMH midcareer investigator award in patient-oriented research (K24). I also have been contributing to the RDoC project at the National Institutes of Mental Health, first as a member of the Negative Valence Systems Workshop, and then as the

Principal Investigator of an NIMH-grant (R01) consistent with the RDoC approach. Finally, I have worked closely with other members of Jiook's mentoring team, including Drs. Posner, Rynn, and Pine.

Jiook is one of the most promising young scientists that I have worked with to date. With a background in engineering and neuroanatomy from Korea, and his PhD and post-doctoral training in neuroimaging in America, he has a unique combination of skills, and he has the drive and creativity to put these skills together in a very innovative way. He has also chosen a very important area of study: the neural mechanisms underlying pathological anxiety. With the K01 training, I am extremely confident that Jiook will become a future leader in our field.

Truly yours,



Helen Blair Simpson, MD PhD  
Professor of Psychiatry at Columbia University Medical Center  
Director of the Anxiety Disorders Clinic and the Center for OCD and Related Disorders at the New York State Psychiatric Institute

## Research Foundation for Mental Hygiene, Inc.

New York Psychiatric Institute Division  
1051 Riverside Drive • New York, New York 10032  
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Feb 2, 2016

Dear Jiook,

I am pleased to fully support your K01 Mentored Research Scientists Award proposal titled, "Neural correlates of fear over-generalization in youth with pathological anxiety". I will happily serve as an advisor as well as a collaborator on your study. I believe that this is an extremely important study aimed at delineating the developmental roots of clinical anxiety. The outcomes of your proposed research will not only impact childhood anxiety disorders, but also adulthood anxiety disorders. I am particularly excited for your inter-disciplinary and trans-diagnostic approach in this proposal to study neurobehavioral mechanisms of youth anxiety disorders. I strongly believe that your prior training at Stony Brook University and Columbia University has prepared you as an ideal candidate for this award.

You have expertise in multimodal neuroimaging and cognitive neuroscience, but I believe additional training in **the phenomenology of anxiety disorders across the lifespan** (from childhood to adulthood) is essential for successful transition to research independence considering your long-term goal of to translate neuroscience to anxiety disorder. As Chief of the Division of Child and Adolescent Psychiatry and Director of the Pediatric Anxiety and Mood Research Clinic and Children's Day Unit, I will provide necessary training in childhood anxiety disorders as follows:

- (1) I will meet with you in **our weekly Research Meetings in the Children's Day Unit (1hr/wk)** at the New York State Psychiatric Institute. In the meetings, you will learn about various clinical cases, research, and therapeutics. I will also arrange your observership for clinical assessments or relevant research activities.
- (2) I will discuss and review the progress of your training in our **monthly one-on-one meeting (1hr/mo.)**.
- (3) As an advisor, I will also coordinate this career development plan with your mentors, Drs. Jonathan Posner and Helen B. Simpson. We will have **quarterly meetings (4hr/yr)** together in person to discuss the progress of your training, research, and career development.

Your application brings together an exceptional candidate and an exciting study. I strongly believe that reception of the K01 Award will allow you to become a future leader in child psychiatry, bridging cognitive, developmental, translational neuroscience, and cutting-edge neuroimaging and data analysis in your research. Moving this field forward requires such innovative, multidisciplinary approaches, and I am delighted to be a part of your training towards achieving this goal.

Sincerely,

Moira Rynn, MD  
Director, Division of Child and Adolescent Psychiatry  
Ruane Professor for the Implementation of Science for  
Child and Adolescent Mental Health (in Psychiatry)  
at the Columbia University Medical Center  
Columbia University, College of Physicians and Surgeons  
New York State Psychiatric Institute



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
Bethesda, Maryland 20892

Dear Jiook,

February 7, 2016

This letter expresses my commitment to working with you as part of your K01 Award, entitled "Neural correlates of fear over-generalization in youth with pathological anxiety". In accordance with NIH policies, the content of letters of collaboration from intramural scientists is restricted to a description of collaborative work proposed under the grant.

I understand that your career development goals focus on an application of translational neuroscience to youth with pathological anxiety to delineate the neural basis of fear over-generalization. I am eager to mentor you on application of fear generalization to youth with pathological anxiety and the concurrent fMRI and psychophysiological experimentations. I have already sent you our fear conditioning paradigms that we have previously used in youth with anxiety disorders. I will continue to provide such consultation and advice during the award period. I will help you examine both the behavioral and fMRI data collected from anxious youth and troubleshoot issues that arise. I will help you interpret your findings in the broader contexts of current neuro-behavioral models of anxiety disorders in youth. This line of research aligns tightly with the focus in my own group and is consistent with other themes emphasized in the larger NIMH research portfolio.

I will happily take an active part in your training in translational, developmental neuroscience research in youth with pathological anxiety as an advisor and a collaborator through:

1. **Hands-on training** in psychophysiological/fMRI experiments in youth with pathological anxiety in my lab at NIMH (1wk/yr);
2. **Monthly meetings via conference calls** to discuss the progress of your training and research (1hr/mo);
3. **Quarterly meetings via conference calls** to discuss the progress of the overall research and career development with your mentors (4hr/yr);
4. **Annual Face-to-face meetings** at conferences (e.g., Biological Psychiatry, ADAA, and ACNP).

Since I am currently employed at the Intramural Research Program of NIMH and would participate as part of my Official Duties, I will not require any compensation for my efforts to assist you. Moreover, no funds from this grant can be used to support any of the work that I conduct as part of my Official Duties. Finally, should you be successful in your application, I do plan to visit you in New York using funds available in my group, and I would be able to support you for a visit to the NIMH to so that I might better assist you in your training.

Best regards,

Daniel S. Pine, M.D.  
Chief, Section on Development and Affective Neuroscience  
National Institute of Mental Health (NIMH)  
Bethesda, MD 20892-1381



BIOSTATISTICS

DuBois Bowman, PhD  
Professor and Chairman

February 3, 2016

Dear Dr. Cha:

I am writing to fully support your proposed research and training outlined in your NIMH K01 proposal, entitled “Neural correlates of fear over-generalization in youth with pathological anxiety”. It is with great pleasure that I support this extremely interesting project, and I will be happy to serve as an advisor and a collaborator on this application. Specifically, I will provide supervision for your training in advanced computational methods in neuroimaging.

My research is committed to develop biostatistical methods to integrate multimodal brain imaging data (including structural, functional, and diffusion MRI) with an aim to determine biomarkers for various psychiatric disorders, such as major depression, schizophrenia, drug addiction, and Parkinson’s disease. Your research focused on multimodal MRI investigating the corticolimbic circuit and function to study pathological anxiety and your training objective (training goal #3) resonates well with my core research interests. Therefore, in the capacity of Chair of the Department of Biostatistics in the School of Public Health at Columbia University, my expertise will complement both your research and your training in this proposal.

**I will meet with you in person on a monthly basis (1hr/mo)** to supervise that component of your training plan (review the training progress and discuss challenges) and to provide hands-on training in the application of advanced statistical and computational approaches that I have been developing (e.g., anatomically weighted functional connectivity integrating diffusion and resting-state functional MRI) to the multimodal MRI data that you are planning to collect in your research proposal. In addition to our monthly meetings, I will collaborate with your mentors (Drs. Posner and Simpson) to ensure the success of your training and career development during the award period. **In quarterly meetings (4hr/yr),** I will review the progress of your research and training with your mentors and other advisors, to ensure that all the goals of this proposal are adequately met.

I believe that your training will prepare you to play a key role in advancing neuroimaging data analysis to develop a biomarker of clinical anxiety in children and adolescents and ultimately to make a significant contribution to the progress of precision medicine in psychiatry. You are an exceptional candidate for this K01 award. I have no doubt that you will become a future leader in this important field. I look forward to working with you soon.

Sincerely,

A handwritten signature in black ink that reads "DuBios Bowman".

DuBios Bowman, Ph.D. Chairman and Professor Department of Biostatistics The Mailman School of Public Health Columbia University



Universität  
Zürich<sup>UZH</sup>

**ETH**

Eidgenössische Technische Hochschule Zürich  
Swiss Federal Institute of Technology Zurich

Institute for Biomedical Engineering  
Translational Neuromodeling Unit

Jiook Cha, PhD  
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3rd Feb 2016

Letter of support for Dr. Jiook Cha, PhD

Dear Jiook,

I am delighted to express my support of your application for a NIMH K01 Award, titled “Neural correlates of fear over-generalization in youth with pathological anxiety”. In my capacity of the Director of Translational Neuromodeling Unit (TNU) at University of Zurich and ETH Zurich, your proposal to combine an fMRI paradigm of fear generalization, multimodal MRI, and computational modeling is of tremendous interest and promise.

My research group is committed to developing computational models of brain dysfunction as tools for better diagnostics or treatment prediction of psychiatric disorders. You are proposing to use a Bayesian learning model, particularly *Hierarchical Gaussian Filtering (HGF)*, a modeling framework recently developed by our group, to investigate maladaptive associative learning during fear generalization in anxious youth. I am excited by this proposal, which could provide much-needed knowledge about the cognitive mechanisms of pediatric anxiety disorders. Building on our close collaboration initiated by your recent NARSAD Young Investigator award, I will provide necessary training so that you will become a leading investigator in Bayesian learning modeling in fear generalization in youth.

As we have already discussed since 2014, I will happily advise and collaborate with you on this exciting project. I will **provide hands-on training on Hierarchical Gaussian Filtering** during your 2-week visit in each year of this K01 award in my lab (**2wk/yr**). During the visits you will learn to implement Hierarchical Gaussian Filtering to analyze the fMRI and behavioral data that you will collect in this K01 research project. In addition to direct training with one of my postdocs who has extensive experience in computational modeling, you will also **participate in my weekly supervision meetings, including the Computational Neuroimaging Clinic**, which deals with practical neuroimaging data analysis problems and our **Translational Neuromodeling Colloquium**. These seminars will provide additional training opportunities for you. Beyond your visit in Zürich, my group and I will provide **continuous consultation via GoToMeeting and email to support your research project (1hr/mo)**. With your mentors and other advisors, I will review and discuss your training and research to ensure that the goals of this proposal are met (**1hr/yr**).

You are undoubtedly an exceptional candidate for this award. I wish you the best of luck and I look forward to working with you on this K01 project as well.

Yours sincerely,

A handwritten signature in black ink, appearing to read "K. E. Stephan".

Prof. Dr. med. Klaas Enno Stephan, PhD  
Director, Translational Neuromodeling Unit



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Computational Science Center  
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phone: (631) 344-3751  
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Feb 1, 2016

Jiook Cha, PhD  
New York State Psychiatric Institute  
Columbia University  
1051 Riverside Drive, Unit 74  
New York, NY 10032

Dear Jiook,

I am very happy to serve as an advisor and collaborator on your K01 Mentored Research Scientist Award entitled, "Neural correlates of fear over-generalization in youth with pathological anxiety". Your study aims to determine fear over-generalization in anxious youth and its neural circuitry using multimodal MRI and computational approaches. I think this is a terrific project and I am delighted to be a part of it.

In my role as an advisor and collaborator, I will **meet you monthly (1hr/mo)** at Stony Brook University in Long Island, NY as we have already done several times or via Google chat throughout the award period. The goal of our work together will be to help you learn and apply cutting-edge big data science approach that has yet to be widely applied to MRI and clinical data in psychiatric research. This includes state-of-the-art predictive modeling using machine-learning algorithms (e.g. Manifold Learning, Bayesian Graphical Modeling, Semi-supervised Network Analysis, etc.) that I have developed and applied to other data-intensive fields, such as bioinformatics, physics, climate science, and social network analysis. I will give you an access to all of these methods. To add to this, I have already given you an access to our core computing system.

Your career development and training thus far have well prepared you for this award. You are an exceptional young scientist and I have no doubt that this award will launch your career as an independent investigator bringing the inter-disciplinary expertise in your field.

Sincerely,

A handwritten signature in black ink, appearing to read "Shinjae Yoo".

Shinjae Yoo, PhD  
Associate Computational Scientist  
Computational Science Center  
Brookhaven National Laboratory

Adjunct Assistant Professor  
Institute of Advanced Computational Science  
Stony Brook University

## **DESCRIPTION OF INSTITUTIONAL ENVIRONMENT**

Columbia University Medical Center and the New York State Psychiatric Institute offer numerous training opportunities, resources for the candidate's career development and research proposed in this K01 application.

### **ENVIRONMENT – Contribution to success**

Dr. Cha and his research team are supported by significant clinical research and imaging resources in the Department of Psychiatry at Columbia University Medical Center 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 Dr. Cha's research team include everything needed to commence 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. Cha) and his mentoring team have offices down the hall from the pediatric neuroimaging laboratory (Dr. Posner), Anxiety Disorder Clinic (led by Dr. Simpson), Pediatric Anxiety and Mood Research Clinic (PAMRC) and Children's Day Unit (CDU; led by Dr. Rynn; see Facilities and Other Resources). 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 Department of Psychiatry, the Division of Child and Adolescent (Dr. Rynn) will ensure the successful recruitment of children and adolescents with anxiety disorders and subthreshold anxiety in this study (see 12. Research Strategy—C2.3. Recruitment Procedures). Furthermore, weekly science meetings at the Anxiety Disorder Clinic, and Children's Day Unit will also provide excellent opportunities for Dr. Cha to learn and collaborate with junior and senior investigators with diverse expertise. 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.

CU/NYSPI maintains an extensive array of departmental and divisional seminars, symposia, and lectures as well as a highly regarded weekly Grand Rounds program providing a forum for renowned researchers to interact with faculty. The MRI Unit, in particular, has a number of resources especially pertinent to the new investigator. Each semester, MRI Unit faculty teaches weekly advanced-level courses in computational modeling of learning and multimodal MRI data analysis. The MRI Unit Meeting occurs once every 1-2 week. This meeting offers a forum for new investigators to interact with MRU personnel and senior investigators, to become apprised of activities, updates, and MRU-related research projects, and as a forum for intellectual exchange through research presentations, and discussion of journal articles.

The research program at CU/NYSPI is exceptionally strong and diverse. This includes work in psychiatry (Drs. David Shaffer, Laurence Greenhill, Hector Bird), eating disorders (Drs. Tim Walsh, Michael Devlin), as well as basic work in neurophysiology (Dr. Eric Kandel), developmental psychobiology (Drs. Myron Hofer, William Fifer), affective disorders (Drs. John Mann, Myrna Weissman), anxiety disorders (Drs. Donald Klein, Michael Liebowitz), schizophrenia (Drs. Jeffrey Lieberman, Claudia Schmauss, Anissa Abi-Dargham), substance abuse (Drs. Herbert Kleber, Edward Nunes), medical genetics (Drs. L. Erlenmeyer-Kimling, James Knowles), and epidemiology (Drs. Myrna Weissman, Ezra Susser, Madeline Gould). **The facilities and resources available to this research team therefore include everything needed for the proposed project and career development.**

## **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 10.8 person months (90% 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 K01 application. His access to the clinical research resources described below is evidenced by his recruitment of 5 youths in his fMRI study on fear generalization (see 12. Research Strategy—C1. Preliminary Studies). His access to the imaging resources in the Department of Psychiatry is also evidenced by these studies, as well as by his recent neuroimaging (structural and diffusion MRI) study with children with ADHD (see Biosketch—Cha). These imaging data were acquired, processed and analyzed (cortical surface analysis and probabilistic tractography) using the MRI scanner at CU/NYSPI and the High-Performance Computing (HPC) system at CUMC (see Facilities and Other Resources).

Research Foundation for Mental Hygiene, Inc.

New York Psychiatric Institute Division  
1051 Riverside Drive • New York, New York 10032  
(646) 774-6500 • (646) 774-6540

**Institutional Commitment to Candidate's Research Career Development**

Feb 16, 2016

We are delighted to provide this letter for Dr. Jiook Cha for the resubmission of his NIMH Mentored Research Scientist Career Development Award (K01). Dr. Cha is an innovative and accomplished young investigator with a passionate commitment to become an independent investigator. On behalf of the New York State Psychiatric Institute and the Department of Psychiatry at Columbia University, we offer our wholehearted commitment to his development as a post-doctoral research fellow in Child and Adolescent Psychiatry.

We are extremely excited about this K01 application, entitled "Identification of Neural Correlates of Fear Overgeneralization in Pathological Anxiety in Youth". In this proposal, Dr. Cha and his mentoring team across multiple Divisions and Departments of CUMC have prepared a comprehensive training plan through which he will develop expertise and gain experience in psychopathology of anxiety disorders; in developmental and translational neuroscience to youth with pathological anxiety; in computational approaches to multimodal MRI. His training program includes structured didactics, private tutorial, and hands-on training that will primarily take place in our institution. Dr. Cha has assembled an impressive team of mentors and advisory committee at our institution—who are highly accomplished investigators in their fields and have extensive experience in the successful mentoring of young investigators. Drs. Posner (primary mentor), Simpson (co-mentor; Director, Anxiety Disorders Clinics), Rynn (advisory committee; Chair, Division of Child and Adolescent Psychiatry), and Bowman (advisory committee; Chair, Department of Biostatistics) at our institution will supervise Dr. Cha's research and training proposal.

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. Cha along this path. Dr. Cha will have access to all the resources within the Division of Child and Adolescent Psychiatry and the Department of Psychiatry, such as office and laboratory space, and related resources. Dr. Cha will also have access to the facilities of the New York State Psychiatric Institute and Columbia University as outlined in his proposal, including the Pediatric Anxiety and Mood Research Clinic, Children's Day Unit, CU Clinic for Anxiety and Related Disorders, and MRI Research Unit. We commit with full assurance that Dr. Cha will have necessary support of his mentors, advisory committee, NYSPI, and Columbia University to collaborate with and recruit community members in his research endeavors. Since Dr. Cha's successful transition to a NIH-funded, independent investigator will be a crucial integral part of our research program, the division and department will provide him with sufficient mentoring and administrative support his successful preparation of R01 in this K01 award period.

In July 2016, it is the Division of Child and Adolescent Psychiatry's intention that Dr. Cha be appointed as an Assistant Professor of Psychiatry in the Division of Child and Adolescent Psychiatry in the Department of Psychiatry at Columbia University and as a Research Scientist at Research Foundation for Mental Hygiene, Inc. The faculty appointment is not contingent upon receipt of this award. We will provide Dr. Cha 90% of protected time to devote to the research and training activities outlined in his proposal upon receipt of his K01.

Dr. Cha has tremendous capability, interest, and drive to become a leader in the field of translational neuroscience and psychiatric research. The Division of Child and Adolescent Psychiatry, the Department of Psychiatry, and the New York State Psychiatric Institute are in an ideal position to provide the vital resources to ensure the successful completion of Dr. Cha's proposed research and training plans. We are fully committed to making available all the essential resources and mentoring to ensure his success.

Sincerely,



Jeffrey A. Lieberman, M.D.

Lawrence C. Kolb Professor in Psychiatry  
Chairman, Department of Psychiatry, Columbia  
University  
Director, NYSPI



Janelle Greenhill, M.P.H.

Director of Administration, Research Foundation for Mental Hygiene, Inc. @ NYSPI

Institutional Commitment



Moira Rynn, M.D.

Ruane Professor for the Implementation of Science  
for Child and Adolescent Mental Health  
Director, Division of Child and Adolescent  
Psychiatry,  
Columbia University/NYSPI

**SPECIFIC AIMS.** Anxiety disorders are collectively one of the most common mental illnesses, affecting about 25% of adolescents and 18% of adults<sup>1</sup>. Symptoms typically begin in childhood or adolescence. Delineating the neural substrates of anxiety in youth, and investigating how the developmental course of these substrates goes awry in the setting of pathological anxiety may lead to identification of neuroimaging markers for early detection and intervention, and the development of novel treatments (*NIMH Strategic Objectives 2 & 3*). Prior studies using fear acquisition and extinction paradigms combined with functional neuroimaging have linked pathological anxiety to a hyperactive amygdala<sup>2</sup>, hypoactive prefrontal cortex (PFC) (e.g., ventromedial PFC [vmPFC])<sup>3</sup>, and their interaction<sup>4</sup> in threat processing. However, mounting evidence implicates fear generalization, and specifically fear **over-generalization**, in pathological anxiety. Fear generalization refers to fear responses that extend to a range of stimuli resembling the original conditioned stimuli<sup>5</sup>. Normal fear generalization serves an adaptive function aiding survival, but in fear **over-generalization**, individuals produce fear responses to a broader range of resembling stimuli. This **over-generalization** may contribute to pathological anxiety by proliferating anxiety cues. Recent studies in adults using laboratory paradigms of fear generalization (e.g., cued fear conditioning) implicate fear **over-generalization** in anxiety disorders, such as generalized anxiety disorder (GAD)<sup>6</sup> and panic disorder<sup>7</sup>. Using a fear generalization task and multimodal MRI, the applicant demonstrated during his PhD training that the vmPFC activates more to safety vs. threat cues<sup>8</sup> in healthy adults. On the contrary, in adults with GAD, vmPFC activation is less discriminating of safety vs. threat cues<sup>9</sup>; in addition, this abnormal vmPFC function is associated with reduced vmPFC thickness and abnormal corticolimbic connectivity<sup>10</sup>.

**Significant questions remain:** (1) Does fear generalization occur in youth, and if so, what neural systems are involved? (2) Does fear **over-generalization** occur in youth with pathological anxiety, and if so, what neural abnormalities are involved? Addressing these questions will lead to subsequent longitudinal research to examine: (3) How does fear generalization and its neural correlates evolve across development? (4) How does pathological anxiety affect these developmental processes? Answers to these questions will promote early detection and novel therapeutics for pathological anxiety. The applicant aims to begin this line of research by addressing questions 1 & 2. Subsequent R01 funded study will address questions 3 & 4. The specific aims are:

**Aim 1: Investigate fear generalization behavior and its relationship to vmPFC function and corticolimbic connectivity in healthy youth (n=25).** We will recruit healthy adolescents (ages 13-17 years old). We will assess the degree to which these individuals generalize conditioned fear by measuring vmPFC activation, self-reported fear, and skin-conductance resistance (SCR) using the fear generalization fMRI task adapted to youth (see 12. Research Strategy). We will assess vmPFC connectivity within the corticolimbic system using diffusion MRI (dMRI)-tractography and resting-state functional connectivity (rsFC).

**Hypothesis 1 (H1)** Healthy youth will generalize conditioned fear: Self-reported fear and fear-potentiated SCR will increase, as cues resemble the 'threat' cue. Conversely, vmPFC activation will increase, as cues resemble the 'safety' cue. **(H2)** Steepness of the vmPFC activation gradient across threat vs. safety cues will correlate with vmPFC connectivity patterns within the corticolimbic circuit as shown in healthy adults<sup>10</sup>.

**Aim 2: Investigate fear over-generalization behavior and its relationship to vmPFC function and corticolimbic connectivity in youth with pathological anxiety (n=50).** We will recruit youth with pathological anxiety, subdivided into a mild-to-moderate anxiety group (n=25) and a moderate-to-severe anxiety group (n=25). We will collect the same measures as Aim #1 (fear generalization fMRI: self-reported fear, SCR, vmPFC activation; multimodal MRI: dMRI and rsFC). This will enable us to examine the behavioral and neural correlates across the spectrum of anxiety symptoms from the healthy (Aim #1) and to anxious youth (Aim #2).

**(H3)** As anxiety severity increases, generalization of conditioned fear will also increase (over-generalization of fear): Self-reported fear, fear-potentiated SCR, and vmPFC activation will show less discriminating responses to threat vs. safety cues. **(H4)** Less discriminating vmPFC activation across threat vs. safety cues (i.e., decreased steepness of the gradient) will correlate with decreased corticolimbic connectivity.

**Exploratory Aim: Assess the impact of development (e.g., age or Tanner stages) and the development-by-anxiety interaction on fear generalization behavior, vmPFC function, and corticolimbic connectivity.**

**Expected Outcomes:** Successful completion of this study will provide cross-sectional evidence of the influence of pediatric anxiety on fear generalization behavior, vmPFC function, and corticolimbic system connectivity. The multiple units of analysis will help elucidate the brain-behavior relationships underlying fear generalization. This demonstration along with the research expertise developed through this K01 award will support an R01, longitudinal study of youth to track developmental trajectories of fear generalization and pathological anxiety. The line of research will promote the development of neuroimaging markers for early detection and novel intervention for pathological anxiety (*NIMH Strategic Objectives 2 & 3*).

## 12. RESEARCH STRATEGY

### A. Significance

**Overview.** Anxiety disorders are extremely common affecting about 25% of adolescents and 18% of adults<sup>1</sup>. Anxiety disorders are associated with substantial functional impairment and economic costs related to lost productivity and treatment. In children, these disorders convey a host of negative outcomes including school refusal, poor academic performance<sup>16</sup>, or increased risks for other mental disorders, such as depression<sup>17, 18</sup>, substance abuse<sup>19, 20</sup>, and ADHD<sup>21</sup>. Though treatments are available, they are often inadequate with response rates typically ranging between 35%<sup>22</sup> and 81%<sup>15</sup> (compared to 24% for placebo). Moreover, there are currently no means of determining which of the available treatments is most likely to be helpful to a particular patient. Lastly, anxiety disorders are typically chronic conditions that either emerge in youth or have developmental antecedents. In youth who display symptoms or risk factors for an anxiety disorder, clinicians are relatively unable to predict who will go on to develop a chronic disorder and whose symptoms will resolve. Therefore, it is critical to understand the neural mechanisms underlying anxiety in youth. This knowledge will not only foster the development of new interventions and preventive strategies, but will also aid in discovering new targets for developing therapeutics.

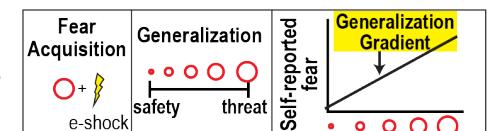
This proposal is significant for the following reasons:

- 1) **Pathological anxiety in youth** is extremely common and is associated with a range of negative outcomes. Understanding the neurobiological substrates underlying pediatric anxiety disorders is critical to developing better interventions (*NIMH Strategic Objective #1–Mechanisms of Complex Behaviors*).
- 2) **Fear over-generalization** is thought to be an important mechanism underlying pathological anxiety in adults; it has never been studied in anxious youth. Understanding fear over-generalization in pediatric anxiety disorders is important in understanding what causes anxiety, how to better diagnose pathological anxiety, and to promote new treatments (*NIMH Strategic Objectives #3–Strive for prevention and cures*).
- 3) **Implementing a dimensional approach to the study of anxiety** is critical to discovering neurobehavioral mechanisms that cut across anxiety disorders; this knowledge will ultimately contribute to a biologically informed psychiatric nosology, eschewing dependence on symptom-based classification (*NIMH Strategic Objective #1–Mechanisms of Complex Behaviors*).
- 4) **Charting the developmental course of anxiety and its neural correlates** is critical for early detection and intervention (*NIMH Strategic Objectives #2–Charting trajectories*). Though this K award is cross-sectional in nature, it will provide data and skills/expertise to inform an R01 proposal for a large-scale longitudinal study tracking changes of fear generalization and the underlying corticolimbic circuit.

**WHY CHILDHOOD ANXIETY DISORDERS?** Approximately 25% of Americans will meet criteria for an anxiety disorder during their lifetime<sup>23</sup>. Anxiety disorders are the earliest psychiatric conditions to manifest, with a median age of onset of 11 years<sup>24</sup>. Since transient fears and anxieties are considered normal development, this developmental expectation often serves to mask the presence of an anxiety disorder<sup>25</sup>. Indeed 80% of kids with a diagnosable anxiety disorder do not receive treatment<sup>26</sup>. Untreated childhood anxiety disorders are associated with considerable functional impairment, such as poor academic performance and school refusal<sup>16, 27</sup>. Childhood anxiety disorders also have adverse long-term outcomes such as increased risks for other negative mental health outcomes over time, such as depression<sup>18</sup> and substance abuse<sup>19, 20</sup>.

**WHY STUDY FEAR GENERALIZATION?** Generalization of fear is a normal adaptive behavior. Humans interpret the perceptual or conceptual details of a learning episode and generalize learned behavior (e.g., fear responses) to different similar stimuli. In this way generalization of fear can serve as a normal adaptive function that aids survival. However, an excessive form of it, **fear over-generalization, can contribute to anxiety pathology, because it proliferates anxiety cues and therefore increases or sustains anxiety symptoms**. Despite its clinical relevance, compared to other associative learning processes linked to pathological anxiety (e.g., extinction/recall<sup>28-30</sup> and fear inhibition<sup>31, 32</sup>), fear generalization has been relatively understudied.

Psychophysiological studies in adults demonstrate that fear over-generalization occurs in various anxiety disorders, such as generalized anxiety disorder (GAD)<sup>6</sup> and panic disorder<sup>7</sup>. These studies used Pavlovian fear conditioning to test generalization effects (**Figure 1**). In this paradigm, participants are typically shown a threat cue (CS+) as well as a range of safety cues that are similar but not identical to the threat cue (never paired with a threat or Unconditioned Stimulus). One can then test a differential response to threat vs. a continuum of safety cues. We will employ a similar fear generalization paradigm adapted to youth (**Figure 5** for preliminary data and **Figure 6** for the study design).



**Figure 1. Pavlovian conditioning paradigm testing generalization of conditioned fear.** After fear acquisition, a generalization effect can be determined by measuring generalization gradients of fear-associated responses (e.g., self-reported fear; see **Figure 3**).

**WHY FOCUS ON vmPFC IN FEAR GENERALIZATION?** *Studies show that in adults with GAD, vmPFC activation is less discriminating of safety vs. threat cues compared to healthy adults.* Our prior fMRI study in healthy adults demonstrated that vmPFC activation during fear generalization shows a steep generalization curve, activated more towards cues similar to a safety cue. This suggests that in healthy adults the vmPFC tracks safety signals (see **Figure 3**)<sup>8</sup>. In contrast, in adults with GAD, vmPFC activation shows a *less* steep generalization curve (hence less discriminating) across the continuum of threat and safety<sup>9</sup>. A less steep vmPFC generalization gradient in adults with GAD correlates with a greater anxiety symptom severity. This suggests that fear over-generalization in adults with GAD is associated with the inability of the brain (i.e., vmPFC) to discriminate threat vs. safety cues. Based on these findings, we will examine the same system in youths with pathological anxiety for the first time (Aim #2).

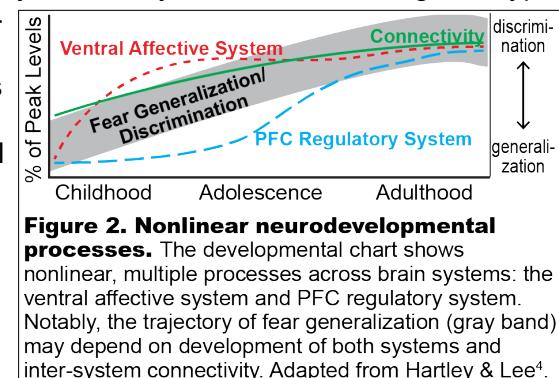
**BRAIN CORRELATES OF FEAR GENERALIZATION.** The vmPFC is considered as an integral hub of the corticolimbic system that mediates emotion and cognitive processes. Within this system *interactions between the excitatory subcortical areas (ventral affective system) and inhibitory PFC areas (PFC regulatory system) are essential for generation of affective meaning in the vmPFC*<sup>33, 34</sup>. The vmPFC *integrates* extensive corticolimbic afferents, *computes* an affective value, and *mediates* an adaptive response. During threat processing, the vmPFC orchestrates several regions within the corticolimbic system: the amygdala<sup>35, 36</sup>, the hippocampus<sup>36-38</sup>, the thalamus<sup>39, 40</sup>, and the prefrontal attentional network<sup>41, 42</sup>. VmPFC function thus may depend upon how it is connected to the corticolimbic circuit.

Our recent study supports this view. In a multimodal MRI study, impaired vmPFC threat-safety discrimination in adults with GAD correlates with multiple factors of the corticolimbic system: (i) decreased vmPFC grey matter thickness, (ii) less positive vmPFC intrinsic functional coupling with the dorsal PFC and more positive coupling with the amygdala, and (iii) decreased structural connectivity of the major white matter tracts encompassing the vmPFC. A structural equation model showed significant impact of these corticolimbic circuit measures on a diagnosis of GAD (see **Figure 4**)<sup>10</sup>. These support the integral role of the vmPFC as a hub node of the corticolimbic system in assessment of threat vs. safety<sup>33</sup>. *Therefore, examining vmPFC fear generalization may offer a useful proxy of how multiple related regions/systems are orchestrated to generate affective meaning (e.g., threat or safety).* We will innovatively use this multimodal MRI approach for the first time to study neural correlates of pathological anxiety in youths.

**WHY STUDY FEAR GENERALIZATION IN YOUTH?** A few studies have examined other fear associative learning processes, such as fear conditioning or extinction. A recent study showed that healthy youth (mean age=11.5 ± 2.57 sd) had comparable fear learning and extinction to adults<sup>43</sup>. An fMRI study demonstrated that preadolescents with anxiety disorders (mean age=9.8 ± 21.2 sd) had greater amygdala activation to fear compared with neutral faces, similar to anxious adults<sup>44</sup>. Based on these studies, it is likely that healthy youth may generalize fear; however, this has been scarcely tested. More importantly, it remains unknown whether pathological anxiety is associated with fear generalization behavior and the corticolimbic system. *Addressing these questions may contribute to public health, in that they may present potential neural markers of pathological anxiety in youth.*

**ANXIETY DISORDERS AS DEVELOPMENTAL DISORDERS.** Pathological anxiety has been primarily defined by symptoms. A recent conceptualization suggests that *only after disruptions of brain circuits do noticeable anxiety symptoms occur*. Thus, early detection of atypical brain development and its relationship with abnormal anxiety behaviors is essential.

Brain development is a nonlinear process (**Figure 2**). Rates of development vary across regions. For example, the ventral affective system (including the amygdala) in youth shows comparable activity to that of adults, whereas the PFC regulatory system including (the ventral and dorsal PFC) in youth is still reaching maturity<sup>4</sup>. These differential developmental rates between the two systems may contribute to changes in typical fear/threat processing across developmental stages. Pathological anxiety may involve abnormal brain developmental processes that contribute to abnormal fear/threat processing. Yet there exists little empirical research linking developmental changes in youths' brains (function, structure, or circuit connectivity) to developmental changes in behavior, cognition, or affect<sup>45, 46</sup>. In this study, we will explore the effect of age on fear generalization and its underlying neural system. Due to the limited scope of a K01 award, we cannot create a comprehensive map of developmental trajectories. Nevertheless, the data and skills/expertise from this award will lead to a future, larger-scale longitudinal study tracking changes



of fear generalization and its underlying corticolimbic circuit.

## B. Innovation

This application is innovative for four reasons:

**1) Novel examination of *fear generalization and the underlying neural substrates in youth*:** No prior studies have examined the neural circuit of fear generalization in youth. This approach will not only provide a cross-sectional perspective on its developmental course, but will also advance our understanding of the neuro-behavioral mechanism of sensitivity to potential threat.

**2) Novel application of *multiple units of analysis*** (behavior, task-fMRI, structural, diffusion, and resting-state fMRI, and self-reports of anxiety symptoms) in youth: No prior studies have combined fear generalization and multimodal MRI in youth with pathological anxiety. This approach will allow linking dysfunction within specific neural regions to anomalies within a neural circuit and to psychology.

**3) A *sampling strategy*** that is both trans-diagnostic (i.e. inclusion of multiple anxiety disorders) and dimensional (i.e., inclusion of normal to abnormal anxiety): No prior studies have used either approach in neuroimaging studies of pediatric anxiety. The transdiagnostic approach will allow examining fear generalization as a *general* mechanism across different anxiety diagnoses; the dimensional approach combined with “metastructure” of DSM-5 anxiety disorders will allow investigating the spectrum of normal to abnormal fear generalization, and thus could link neuroscience to psychopathology of pediatric anxiety.

**4) The proposed training plan is *highly interdisciplinary and novel*** in the field of child psychiatric research, because it combines expertise in (i) psychopathology of anxiety disorders, (ii) patient-oriented, translational, and developmental neuroscience of anxiety, and (iii) computational approach to multimodal MRI. This will be an excellent training vehicle for translational neuroscience research studying pathological anxiety.

## C. Approach

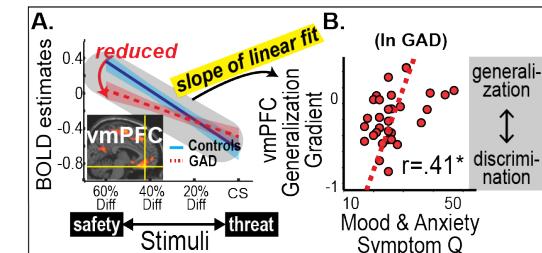
**C1. Preliminary Studies.** This section describes pilot data supporting the design and feasibility of the proposed project: The applicant's previous studies demonstrate that (1) in healthy adults the vmPFC activation tracks safety signals<sup>8</sup>, (2) in adults with GAD the vmPFC activates less to safety but more to threat signals<sup>9</sup>, (3) in both healthy adults and adults with GAD, the fidelity of the vmPFC threat-safety discrimination is closely linked to connectivity of the corticolimbic system<sup>10</sup>. The applicant's pilot data also shows (4) validation of the fear generalization fMRI task in youth with pilot data in five cases.

**1. VMPFC activation tracks safety signals in healthy adults (n=25).** In the applicant's PhD study, young healthy adults (ages 18-24 years) were tested on a fear generalization fMRI task. VmPFC activation tracked safety signals<sup>8</sup> (**Figure 3A**; solid line). This supports the feasibility of using fear generalization fMRI to study vmPFC threat processing (Aim 1).

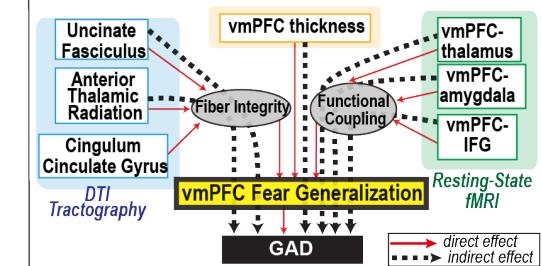
**2. Abnormal vmPFC function in adults with GAD (n=32).** Adults with GAD showed less discriminating vmPFC generalization gradient across threat vs. safety cues—that is, reduced activation to safety cues—, compared with HC<sup>9</sup> (**Figure 3A**; dotted line). A less discriminating vmPFC generalization gradient, in adults with GAD, correlates with greater anxiety symptom severity (**Figure 3B**). These findings demonstrate that abnormal vmPFC function is linked to GAD in adults. This K01 will investigate this link in youth with pathological anxiety for the first time.

**3. Abnormal vmPFC function associated with abnormal corticolimbic circuit.** Using multimodal MRI, the applicant showed during his PhD training that, in adults with GAD, specific abnormal corticolimbic circuit measures have impact on abnormal vmPFC activation during fear generalization (a direct effect; red solid line in **Figure 4**) as well as on the diagnosis of GAD (an indirect effect; black dotted line)<sup>10</sup>. This suggests that abnormal corticolimbic connectivity may be associated with psychopathology of adulthood anxiety disorders via its impact on the vmPFC function.

**4. Validation of fear generalization fMRI in youth.** In a pilot study of fear generalization fMRI, healthy youth (n=5; age 11-17 years; mean=15.2) showed significant generalization gradients in self-reported fear and activation of the corticolimbic system (**Figure**



**Figure 3. A, VMPFC activation plotted as a function of stimuli.** Healthy adults showed greater vmPFC activation to safety than to threat (solid line). Steepness of this activation gradient was significantly reduced in GAD (dotted line). **B, A scatter plot showing association between vmPFC generalization gradient and anxiety symptom severity in GAD** (anxiety subscale in Mood & Anxiety Symptom Qnr1). \* $p < .05$



**Figure 4. VMPFC threat processing is associated with multivariate patterns of the corticolimbic circuit.** Only significant paths are shown ( $p < .05$ ). Methods: Structural Equation Modeling.

5). VmPFC activation tracked safety signals showing greater activation towards the safety cues (i.e., cues 60% different [small or bigger] from the conditioned stimulus [CS]). These data support that youth may generalize fear.

**C2. Research Plan** The overall objective of this proposal is to test the impact of pathological anxiety in youth on fear generalization behavior and the underlying corticolimbic function and connectivity. To this end, we propose a multimodal MRI study combined with a fear generalization fMRI task in youth (ages 13-17 years) across the spectrum of anxiety, from normal to abnormal. In Specific Aim #1, we will investigate fear generalization behavior (using self-reported fear and fear-potentiated SCR) and its relationship with corticolimbic function (vmPFC activation) and connectivity (diffusion tractography and resting-state functional connectivity [rsFC]) in healthy youth (n=25). In Specific Aim #2, we will investigate fear over-generalization behavior and its relationship with vmPFC function and corticolimbic connectivity in youth with pathological anxiety (n=50).

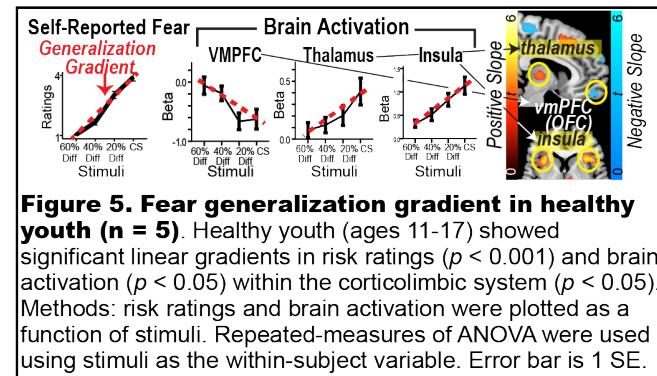
#### **C2.1. Subjects.** Adolescents (n=75) will be recruited across 3 anxiety symptom levels:

- The anxiety levels will be based on Pediatric Anxiety Rating Scale<sup>47</sup> (PARS; range 0-30): (1) low-to-mild anxiety (PARS≤12; n=25; Aim #1); (2) mild-to-moderate anxiety (13≤PARS≤19; n=25; 13 is considered clinically meaningful anxiety; Aim #2); (3) moderate-to-severe anxiety (20≤PARS; n=25; the criterion used in the Child/Adolescent Anxiety Multimodal Study<sup>15</sup>; Aim #2).
- Subjects will be group-matched on age<sup>48</sup>, Tanner Stage, sex<sup>49</sup>, and handedness<sup>50</sup>.
- Inclusion criteria are (1) ages 13-17 years and (2) medication-free for a minimum of 2 months prior to the study. Exclusion criteria are (1) current DSM-5 disorder other than an anxiety disorder, (2) MRI contraindication, (3) history of major neurological or medical illness or head trauma with>10 min loss of consciousness, (4) history of substance dependence; (5) IQ<80 (Wechsler Abbreviated Scale of Intelligence).

**C2.2. Key Design Decisions.** The current proposal is designed to generate pilot data to inform a future R01 longitudinal study tracking developmental changes of fear generalization from children to young adults using a dimensional and trans-diagnostic approach. **(1) New selection of ages 13-17 years.** Fear generalization has been tested in adults in previous studies (young adults with ages 18-24 years in the applicant's PhD study), but few reports exist in adolescents. **(2) Trans-diagnostic sampling.** In previous studies fear generalization is shown in adults with various anxiety disorders<sup>7, 51, 52</sup>. This study will begin to study fear generalization in youth across anxiety disorders, starting with the most common triad of anxiety diagnoses in youth—GAD, Social Phobia, and Social Anxiety Disorder—, which are highly comorbid<sup>38</sup>. **(3) Dimensional sampling.** We chose to focus on the dimension of anxiety severity, rather than diagnosis, in keeping with the NIMH Strategic Plan and the RDoC initiative. **(4) Measures of development.** Although the primary and secondary aims of this proposal are to investigate fear generalization and the corticolimbic circuit correlates (Aim 1), and to investigate fear over-generalization and the corticolimbic circuit correlates in youth with pathological anxiety (Aim 2), the exploratory aim is to assess the impact of development and its interaction with sex on the behavioral and neural measurements. To this end, we will use age as a primary measure (as in youth MRI studies<sup>48, 53</sup>), and Tanner Stage (see C2.5. Experimental Procedures) as a supplementary measure. This exploratory aim may potentially be underpowered, but will inform the design of a future large-scale R01 investigation.

**C2.3. Recruitment Procedures.** Participants will be recruited through: (1) word-of-mouth, (2) advertisements placed in local media, (3) referrals from medical and mental health professionals, (4) online participant recruitment tools (e.g., ResearchMatch®, a free national research participant). Advertisements will be placed in community newspapers and in community settings (e.g., churches), and on the websites, including the CUMC Psychiatry Research website, Anxiety Disorders Association of America, Facebook, and Google AdWords (see Budget Justification). Brochures will be sent to clinicians (mental health professionals including school counselors, pediatricians), and local parent support groups. We will post flyers throughout New York City and the surrounding suburbs. In order to enhance retention, we will schedule appointments in advance and make every effort to accommodate the participant's schedule (e.g., weekends or after-school hours), and give multiple reminders by phone, mail, email or text message (e.g., the night before scheduled appointments). On an appointment day, taxi service may be arranged to ensure timely arrival of participants.

Referrals will be provided through the **Pediatric Anxiety and Mood Research Clinic (PARMC)** and the **Children's Day Unit (CDU)**, directed by Dr. Rynn (advisor); **CU Clinic for Anxiety and Related Disorders (CUCARD)**, of which Dr. Rynn is the medical director; the **Anxiety Disorders Clinic**, directed by Dr. Simpson



**Figure 5. Fear generalization gradient in healthy youth (n = 5).** Healthy youth (ages 11-17) showed significant linear gradients in risk ratings ( $p < 0.001$ ) and brain activation ( $p < 0.05$ ) within the corticolimbic system ( $p < 0.05$ ). Methods: risk ratings and brain activation were plotted as a function of stimuli. Repeated-measures of ANOVA were used using stimuli as the within-subject variable. Error bar is 1 SE.

(advisor); the **Children's Anxiety & Depression Clinic at Children's Hospital of New York at Presbyterian Medical Center (CHONY)**, where Drs. Posner and Rynn work closely with staff (see Facilities & Other Resources). These recruitment sites can provide referrals across the **range of anxiety symptom severity**: Over the past 2 years, adolescents in the CDU have had PARS total scores from 10 to 27 (mean=19). Also, these recruitment sites can provide referrals of **comorbidity- and medication-free anxious adolescents**: In 2014, 300 new adolescents were referred for anxiety disorders without comorbid disorders at CHONY. With a conservative estimate of 50% that will meet our inclusion/exclusion criteria, in this site alone, 150 adolescents per year will be eligible for this study. This rich clinical research environment will facilitate recruitment.

**C2.4. Clinical Assessments.** **General assessment.** Children who meet the study criteria will be assessed using Anxiety Disorders Interview Schedule-Revised (ADIS-R<sup>54</sup>) by a on-site clinician in the CDU of the NYSPI (Drs. Rynn or Goldberg). Female Menstrual Cycle will be assessed<sup>55</sup>. **Anxiety symptoms:** We will use Pediatric Anxiety Rating Scale (PARS<sup>47</sup>), State Trait Anxiety Inventory for children (STAIC<sup>56</sup>), Screen for Child Anxiety Related Emotional Disorders (SCARED<sup>57</sup>). **Other mood symptoms:** Children's Depression Inventory (CDI<sup>58</sup>).

**C2.5. Experimental Procedures.** After screening and providing consent, Tanner stages will be assessed by an on-site clinician at CU/NYSPI (Drs. Moira Rynn or Jonathan Posner, MD)<sup>59</sup>. Participants will undergo a mock scanner session to adjust to the scanner. Participants will then undergo multimodal MRI scanning; frequent praise and reminders will be used to help participants remain awake and still. We will perform the following ~45-min MRI scan: structural-5min, fear generalization-15min, diffusion-8min, and resting-state functional MRI (eyes-open)-10min. To control for **variations of hormonal status for menstruating participants**, MRI sessions will be scheduled to their early follicular phase. To control for **diurnal variation** (e.g., hormones<sup>60</sup>), MRI will be scheduled at the same time (e.g., 5PM after school hour).

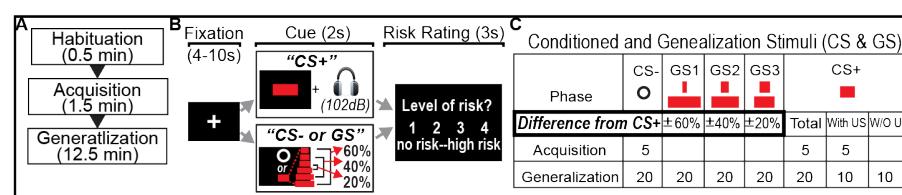
**C2.6. Fear Generalization fMRI Task.** Inside the MRI scanner, participants will complete a 15-min fear generalization task. Of note, we will use an instructed fear generalization paradigm (i.e., participants will be informed of CS-US (unconditioned stimulus) contingency before the task), because it allows minimizing the iteration of stimuli representation to produce a robust CS-US pair and robust generalization of conditioned fear<sup>9, 61</sup>. The task consists of habituation, acquisition, and generalization (**Figure 6A**). The entire task is conducted inside the MRI scanner but

participants will be scanned only during the generalization phase, the phase of our interest. **For a habituation phase**, participants will hear an auditory startle probe (40msec, 102dB<sup>62</sup>) six times without any visual cues to order to minimize startle-caused head motion. The startle probe will serve as the Unconditioned Stimulus (US). Next, for

**an acquisition phase**, participants will be instructed on CS-US contingency: Presentation (2sec) of a mid-sized rectangle (56 pixels in height and 280 pixels in width) will be paired with the auditory startle probe (occurring 1.9s after the onset of the rectangle). This rectangle will thus serve as CS+. Participants will then view a white ring without a startle (CS-), and the mid-sized rectangle (CS+) presented in a pseudo-random order. During the presentation, CS+ will be always paired with the US to induce rapid fear acquisition. Lastly, **for a generalization phase**, the same CS+ (the mid-sized rectangle) and CS- (the white ring) will be used, and 6 other rectangles of identical height (56 pixels) but with varying widths (112-448 pixels) also will be used. The 6 rectangles will differ by ±20%, ±40% or ±60% in width from the CS+. Note that, for GS, widths are counter-balanced. These rectangles will never be paired with the US; thus they will serve as the generalization stimuli (GS).

**Altogether, these create a continuum of threat and safety.** During generalization, we will present pseudo-randomly a stimulus followed by a jittered fixation cross. This will be followed by a risk rating on a 4-point scale using a button box (**Figure 6B**).

**C2.7. Data Acquisition. MRI.** Participants will be scanned with a 3T GE Signa scanner with 32-channel head coil at CU/NYSPI. We will collect **rs-fMRI**, **SMRI** and **DMRI** as in the applicant's previous study<sup>13</sup> (**Table 1**). **Self-Reported Fear.** Participants will rate their perceived fear or risk immediately after viewing each stimulus on a four-point Likert scale using a MR-compatible button box. **Fear-potentiated SCR.** SCRs will be collected from the second



**Figure 6. Fear generalization fMRI task.**

A, Overall plan. B, Generalization phase. C, Trial types and frequencies during the study: For an acquisition phase, only CS+ or CS- will be presented. For a generalization phase, all the stimuli (CS+, CS-, and GS) will be presented.

**Table 1. Pulse sequences of multimodal MRI**

fMRI	T2*-weighted echo planar images, TR=2000ms, TE=23ms, FOV=224 mm, slices=37, voxel-size= 2.33×2.33×3.5 mm, volumes: 300 for <b>fear generalization task</b> ; 150 for <b>rs-fMRI</b> (2 sessions).
SMRI	fast-spoiled gradient-recall sequence, 256 × 256 matrix; FOV=250 mm; 1 mm isotropic
dMRI	TR=8500ms; FOV=240 mm; voxel size=1.7×1.7×2.5 mm; 60 slices; 25 non-collinear directions (b = 1,000 s/m <sup>-2</sup> )

and third digits using a MR-compatible electrodermal activity recording system. SCR will be scored if the trough-to-peak response begins 1-4s after stimulus onset, lasts 0.5-5.0s with amplitude greater than 0.02 microsiemens<sup>43, 63</sup>. Scored SCRs will be normalized in each individual to compare across subjects<sup>64</sup>.

**C2.8. Image Processing.** We will use the same image processing procedures in the applicant's recent publications<sup>10, 13, 61, 65, 66</sup>. Briefly describing, for **Task-fMRI**, we will perform slice timing correction, motion correction (motion parameters will used in GLMs as nuisance variables), spatial normalization, smoothing in SPM12 (Statistical Parametric Mapping), and physiological noise correction<sup>67</sup>. For **rsFC**, after the same pre-processing, voxel-wise seed based correlation will be applied using the CONN toolbox<sup>68</sup>. For **DMRI**, we will perform eddy current correction, rotation of gradient matrices, and diffusion tensor model fitting, and Bayesian estimation of diffusion parameters. **Probabilistic tractography** will be performed because it offers more reliable tract estimation than a deterministic method<sup>69</sup>.

**C2.9. Data Analysis 1–Risk ratings and fMRI. Risk Ratings.** We will build a group-level GLM containing group (anxiety levels) as the factor (for Aim #2), and the nuisance covariates (e.g., sex, age [primary], Tanner stage [secondary], BMI, ethnicity, handedness, and IQ). **fMRI.** We will use an established method to test generalization effects<sup>8–10, 61</sup>. First, preprocessed images will be entered into a subject-level GLM in SPM12. Regressors of interest include onsets of GS 60%, GS 40%, GS 20%, CS+, CS-; and nuisance covariates include in-scanner motion parameters. Planned contrasts are 'each condition vs. rest'. To test generalization effects, we will use the four contrast images (GS60%, GS40%, GS20%, and CS+) as the dependent variable in a group-level GLM, including the nuisance covariates above. Linear trend of the fear generalization gradient will be estimated using a contrast of '1.5 0.5 -0.5 -1.5' within a vmPFC region of interest (ROI; defined by an atlas<sup>10</sup>). **Fear generalization gradient.** Parameter estimates will be obtained across the individuals for the subsequent correlation analyses, based on a peak voxel showing a significant fear generalization gradient<sup>10</sup> (**Figure 3 & 5**).

**C2.10. Data Analysis 2–dMRI and rsFC.** We will estimate structural and functional connectivity of the corticolimbic system using dMRI and rsFC. **ROI definition.** ROIs for the connectivity analysis will be defined using structural segmentation results in Freesurfer. These include vmPFC (the medial orbital frontal gyrus in Desikan atlas<sup>70</sup>, previously used in fear generalization<sup>10</sup> and fear extinction studies<sup>30</sup>), the PFC regulatory regions (e.g., the dorsolateral PFC and ACC) and, the ventral affective subcortical regions (e.g., the amygdala, hippocampus, caudate, striatum, and brainstem) based on a prior fear generalization study<sup>10</sup>. **Seed-based connectivity mapping.** Using the vmPFC as a seed, we will perform diffusion probabilistic tractography and rsFC following the methods used by the applicant<sup>10, 13, 65, 66</sup>. **GLMs.** We will examine whether the corticolimbic connectivity measures correlate *vmPFC fear generalization gradients* (**Figure 3 & 5**). **For dMRI**, a GLM will contain vmPFC fear generalization gradients as the dependent variable; probabilistic tractography measures as the independent variable; and the nuisance covariates (e.g., sex, age [primary], Tanner stage [secondary], BMI, ethnicity, handedness, and IQ). **For rsFC**, a GLM will contain vmPFC-seeded connectivity maps (parameter estimates) to the ROIs as outcome variable; vmPFC fear generalization index as the predictor; sex, age, BMI, ethnicity, and IQ as the covariates. Alternatively, we will apply network-based statistics (NBS)<sup>71</sup> as in the applicant's previous study<sup>13</sup> to control family-wise error rates for correlated connectivity. Lastly, GLMs will be used to determine correlation between vmPFC fear generalization estimates and corticolimbic connectivity.

**C2.11. Bayesian Learning Modeling:** In order to infer learning mechanisms (e.g., prediction error of threat) underlying fear over-generalization in youth, we will apply Hierarchical Gaussian Filter (HGF)<sup>72, 73</sup> to self-reported fear, SCR, fMRI. Of note, an advantage of HGF is that it allows estimating *subject-specific learning parameters*<sup>72, 73</sup>. We will first estimate 'precision-weighted' prediction error from each individual's self-reported fear or SCR<sup>74</sup>; then, these estimates will be used to determine brain activation correlates as a parametric modulator in the group-level GLM of task fMRI.

**C2.12. Hypothesis Testing and Power Analysis. Aim 1: Investigate fear generalization behavior and its relationship with vmPFC function and corticolimbic connectivity in healthy youth (n=25). Hypothesis 1:** Healthy youth will generalize conditioned fear: Self-reported fear and fear-potentiated SCR will increase, as cues resemble the 'threat' cue. Conversely, vmPFC activation will increase, as cues resemble the 'safety' cue. **H1-Methods:** We will use GLMs with stimulus as the within-subject factor and with self-reported fear, SCR, or vmPFC activation as the dependent variable in each model, respectively.  $P<.05$  will be considered significant; in the voxel-wise vmPFC activation analysis, we will use the false discovery rate to correct  $p$ -values, and a corrected  $p<.05$  will be considered significant. **H1-Power Analysis:** Based on the effect size  $f$  of .97 (partial  $\eta^2=.49$ ) of linear effect of the linear gradient of the vmPFC activation in the applicant's prior study in healthy adults<sup>8</sup>, when power  $>.95$  and alpha  $<.01$ , the required sample size is 15. Our planned sample of 25 may be sufficient. **Hypothesis 2:** Steepness of the vmPFC activation gradient across threat vs. safety will

correlate with vmPFC connectivity patterns within the corticolimbic circuit. **H2-Methods:** We will use GLMs with generalization index of vmPFC activation as the independent variable, and functional and structural connectivity of the corticolimbic system as the dependent variables, respectively in separate models. The false discovery rate will be used to correct *p*-values for multiple comparison and a corrected *p*<.05 will be considered significant. **H2-Power Analysis:** In our prior study with young adults, a hierarchical regression analysis showed the corticolimbic circuit measures (e.g., diffusion tractography, and rsFC) significantly explained vmPFC fear generalization index—with an adjusted  $r^2$  of 0.565, equivalent to Cohen's *f* of 1.3. Based on this effect size, with power>0.80 and alpha<0.05, we require a sample size 18. This justifies our planned sample size of 25. **Possible Confounds:** In-scanner head motion estimates, sex, age (primary), Tanner stage (secondary), BMI, handedness, and IQ will be used as the nuisance variables in extended models. **Exploratory Analyses: Model-Based fMRI**—We will assess brain activation associated with the learning parameters (e.g., precision-weighted prediction error) from HGF. The parameters will be used as the parametric modulator in a GLM for fMRI. Effects of anxiety symptom severity on the brain activation will be then examined.

**Aim 2: Investigate fear over-generalization behavior and its relationship with vmPFC function and corticolimbic connectivity in youth with pathological anxiety (n=50).** **Hypothesis 3:** As anxiety severity increases, generalization of conditioned fear will also increase (over-generalization of fear): Self-reported fear, fear-potentiated SCR, and vmPFC activation will show less discriminating responses to threat vs. safety cues.

**H3-Methods:** To assess impact of anxiety on the generalization gradients, we will perform ANOVA or MANOVA (multivariate ANOVA). Fear generalization gradients of self-reported fear, SCR, and vmPFC activation will be used as the dependent variables, in a separate GLM, respectively; and anxiety group, as the independent variable. We will consider *p*<.05 as significant. **H3-Power analysis:** Based on the effect size *f*=.24 ( $\eta^2=.06$ ) of the interaction between within-subject (stimulus) x between-subject (group) factors in repeated measures of ANOVA in the applicant's prior study in adults with GAD<sup>9</sup>, a sample size of *n*=75 will provide adequate power (>.95) to detect an alpha<.01. **Hypothesis 4:** Less discriminating vmPFC activation across threat vs. safety cues (i.e., decreased steepness of the gradient) will correlate with decreased corticolimbic connectivity. **H4-Methods:** Same as in H2, we will use GLMs with generalization index of vmPFC activation as the independent variable, and functional and structural connectivity of the corticolimbic system as the dependent variables, respectively in separate models. **H4-Power Analysis:** As in H2, the sample size of *n*=75 is adequately powered (> .95) to detect an alpha <.01, based on the effect size in the applicant's prior study.

**Possible Confounds:** In addition to the nuisance covariates as in Aim #1, we will also include depression scales as a covariate, given frequent comorbidity with anxiety<sup>75, 76</sup>.

**Exploratory Aim: Assess impact of development and the interaction of development-by-anxiety on fear generalization behavior, the corticolimbic function and connectivity.** Given the age range (13-17 years) in this proposal, development may affect fear generalization and the corticolimbic system. Furthermore, pathological anxiety may impact the normal development. **Method:** (1) **GLMs. Healthy youth (n=25)**—In a multivariate GLM with self-reported fear, SCR, vmPFC activation, and corticolimbic connectivity, as the outcome variables, we will include age (primary) and Tanner Stage (secondary) as the predictors, sex-by-age (alternately Tanner stage) interaction, and the nuisance variables above. **Healthy & anxious youth (n=75)**—In the same multivariate GLM, we will add 2-way interaction between development and anxiety.

**C3. Anticipated Problems and Alternative Strategies.** (1) In exploratory aim, if the GLMs fail to show a significant interaction of development-by-anxiety on vmPFC fear generalization gradients or the corticolimbic connectivity measures, we will alternatively use continuous variables of anxiety symptom scales instead of the categorical anxiety group variable. For anxiety scales, we will first select scales significantly predicting the neural measures in a stepwise manner, and then model the interaction with development. (2) Regarding the correlation between vmPFC fear generalization and corticolimbic connectivity, power may be lost because of multiple comparisons. If so, we will use multivariate partial least square regression as in the applicant's recent study<sup>13</sup>. This will allow identifying patterns of the entire connectivity matrix, instead of treating each measure as an independent variable. (3) It is possible that generalization effects in healthy youth or over-generalization in anxious youth may be masked by significant sex differences in threat processing and its developmental trajectories<sup>49</sup>. If so, we will add the following interaction terms in the GLMs: 2-way interaction of sex-by-anxiety and 3-way interaction of sex-by-anxiety-by-development. Alternatively, we will examine each sex separately.

**C4. Expected Outcomes and Future Directions.** **Aim 1. Investigate fear generalization behavior and its relationship with vmPFC function and corticolimbic connectivity in healthy youth.** We expect to demonstrate for the first time that healthy youth show normal fear generalization measured through behavior and MRI and to delineate the neural correlates of this behavior. **Aim 2: Investigate fear over-generalization behavior and its relationship with vmPFC function and corticolimbic connectivity in youth with patho-**

***logical anxiety.*** We expect to demonstrate for the first time that anxiety symptom severity in youth, irrespective of diagnosis, correlates with fear over-generalization measured through behavior and MRI. These outcomes are important because they will support the theory that fear over-generalization is one mechanism underlying pediatric anxiety. **Future Directions.** These outcomes will lead to a larger-scale R01-funded study to longitudinally track developmental changes of fear generalization using trans-diagnostic, dimensional sampling with the aim of identifying a ‘tipping point’ marking the transition from normal to pathological anxiety or disruptions in brain development. The long-term goal of this line of research is to promote early detection, prevention, and new interventions for youth with pathological anxiety.

## PROTECTION OF HUMAN SUBJECTS

**1. Involvement of Human Subjects.** We will recruit three groups of adolescents (n=75): non-anxious youth (n=25), those with subthreshold anxiety (n=25), and those with DSM-5 anxiety disorders (n=25). We will not target a specific N for each subcategory of the DSM-5 anxiety spectrum disorder because of the limited research budget in K01 award. Both females and males will be recruited and we will group match the subjects for important biological or other variables, such as age, Tanner stage, sex, and handedness.

75 youths will be recruited across 3 anxiety symptom levels. The anxiety symptom levels will be based on clinician-rated Pediatric Anxiety Rating Scale (PARS)<sup>47</sup> and will consist of:

- 1) Low-to-mild anxiety (PARS ≤ 9; n=25);
- 2) Mild-to-moderate anxiety (10 ≤ PARS ≤ 15; n=25);
- 3) Moderate-to-severe anxiety (16 ≤ PARS; n=25).

All subjects will meet the following inclusion criteria:

- 1) Ages of 13-17 years;
- 2) Medication-free for a minimum of 2 months prior to participation in the study.

All subjects will meet the following exclusion criteria:

- 1) Current DSM-5 disorder other than an anxiety disorder, such as PTSD, OCD, Bipolar Disorder, Psychotic Disorder, Substance Use Disorders, or ADHD;
- 2) Contraindication to an MRI scan;
- 3) History of major neurological or medical illness or head trauma with >10-minute loss of consciousness;
- 4) History of substance dependence;
- 5) IQ<80 (Wechsler Abbreviated Scale of Intelligence).

**2. Sources of Research Material.** Research material will include: (1) MRI scans; (2) neuropsychological testing; and (3) questionnaires measuring demographic characteristics such as age, sex, medical history, medications, psychiatric history, substance abuse history, and parental occupation, as well as clinician ratings and diagnostic interviews.

**3. Recruitment Procedures.** We will recruit 25 adolescents with mild-to-moderate (subthreshold) anxiety and 25 with moderate-to-severe anxiety (a DSM-5 anxiety disorder) through the following resources:

- 1) Word-of-mouth;
- 2) Advertisements placed in local media;
- 3) Referrals from medical and mental health professionals;
- 4) Online participant recruitment tool

Advertisements will be placed in community newspapers and in community settings (e.g., churches), and on the websites, including the CUMC Psychiatry Research website, Anxiety Disorders Association of America, Facebook, and Google AdWords. Brochures will be sent to clinicians (mental health professionals including school counselors, pediatricians, and local parent support groups). We will post flyers throughout New York City and the surrounding suburbs. In order to enhance retention, we will schedule appointments in advance and make every effort to accommodate the participant's schedule (e.g., weekends or after-school hours), and give multiple reminders by phone, mail, email or text message (e.g., the night before scheduled appointments). On an appointment day, taxi service may be arranged to ensure timely arrival of participants.

Referrals will be provided through the Pediatric Anxiety and Mood Research Clinic (PARMC) and the Children's Day Unit (CDU), directed by Dr. Rynn (advisor); CU Clinic for Anxiety and Related Disorders (CUCARD) at CU/NYSPI, of which Dr. Rynn is the medical director; the Anxiety Disorders Clinic, directed by Dr. Simpson (advisor); the Children's Anxiety & Depression Clinic at Children's Hospital of New York at

Presbyterian Medical Center (CHONY), where Drs. Posner and Rynn work closely with staff (see Facilities and Other Resources). These recruitment sites can provide referrals across the range of anxiety symptom severity: e.g., over the past 2 years, adolescents in the CDU have had PARS total scores from 10 to 27 (mean=19). Also, these recruitment sites can provide referrals of comorbidity- and medication-free anxious adolescent: e.g., in 2014, 300 new adolescents were referred for anxiety disorders without comorbid disorders at CHONY. With a conservative estimate of 50% that will meet our inclusion/exclusion criteria, in this site alone, 150 adolescents per year will be eligible for this study. This rich clinical research environment will facilitate recruitment.

**4. Consent Procedures** Consent and assent for the study procedures will be obtained from both the parent and youth. Parents will be informed that all data collected about the child is confidential and that no information will be shared with the parent. For subjects who meet preliminary eligibility criteria, structured diagnostic interviews will be collected from both the youth and parent by Dr. Posner or an on-site clinician in the Children's Day Unit (CDU) of the NYSPI. General interviews of the child and parent will provide social, academic, and medical functioning. Neuropsychological assessment and MRI studies will also be collected from the youth. No personally identifying information will be collected in the questionnaires, interviews, or other research materials thus assuring confidentiality. Moreover, subject identification numbers will be assigned to each participant and will be used to label research materials. All data will be stored in locked file cabinets or password-protected computers in a locked office at the New York State Psychiatric Institute (NYSPI).

**5. Potential Risks** The risks associated with MRI scanning can be classified into one of four categories: 1) Acoustic Noise Levels, 2) Gradient or Time-Varying Magnetic Fields, 3) Radiofrequency (RF) Magnetic Fields, and 4) Static Magnetic Fields.

- 1) Acoustic Noise** 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 just 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.

**2) 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 no significant risk to the participant.

**3) 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  $\square$  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 it 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.

**4) 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 no significant 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.

### **5) Possible Incidental Risks**

**Potential distress during fear generalization experiment** The aversive nature of the generalization task as well as the physical confinement and isolation inside the scanner could potentially cause minimal to mild emotional distress. For example, repetitive exposure and anticipation of aversive stimulus (i.e., an acoustic startle probe--white noise) during the task could potentially induce mild distress to vulnerable participants. Of note, however, the unconditioned stimulus we plan to use in this proposal is designed to induce a startle, rather than a strong emotional response, such as fear; hence, it has been favorably used in previous studies in more vulnerable samples<sup>62</sup>. In our past experience with the healthy adolescents (ref. 12. Research Strategy—preliminary studies), all the participants tolerated the entire procedures well. The participants rated their level of discomfort as mild in post-task rating. Similarly, in our previous studies in adults with generalized anxiety disorder, the patients rated the fear generalization task, in which we used even a more potent unconditioned stimulus—electric shock—as “mildly to moderately aversive”. Most importantly, the institutional review board at the NYSPPI has approved our fear generalization protocol. Taken together, the incidental risks are deemed non-significant. My primary mentor, Jonathan Posner, MD, is a board certified child and adolescent psychiatrist. Though we feel this is extremely unlikely, Dr. Posner will be available to talk with participants and their families should any participant experience excessive distress or anxiety.

**Distress due to other procedures.** There is a risk of distress stemming from the detailed psychiatric history obtained during screening and diagnostic interviews. In our experience, however, participants have tolerated this well.

### **6. Protecting Against Potential Risks** Our 3.0 Tesla scanner satisfies FDA criteria for non-significant risk (NSR) in all risk categories:

**Acoustic Noise:** As suggested by the FDA, I 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 I intend to do for all scans. I will also be using acoustically shielded headsets, which further attenuate noise.

**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, I 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, I 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:

- a) Inform the subject that peripheral nerve stimulation may occur
- b) Describe the nature of the sensation to the subject
- c) Instruct subjects not to clasp their hands, since this may create a conductive loop which will increase the possibility of stimulation

- d) Maintain constant verbal contact with the subject
- e) Instruct subjects to inform the MR technologist if they experience discomfort or pain
- f) Terminate the scan if the subject complains of discomfort or pain
- g) 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.

SAR Absorption 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 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.

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, and like other clinical MRI centers, our facility will incorporate a complete range of procedures to assure security of the restricted access area, careful screening of potential subjects before they enter the restricted access area, and a metal detector positioned at the doorway leading into the magnet room within the MRI suite. Access to the MRI suite will be tightly controlled, allowing access only to personnel and research subjects who have legitimate reason to be there. Doors to the unit will be 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 prostheses, pins, clips, IUD's, etc.

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.

Confidentiality All the information obtained from the subjects will be coded by number and kept in locked, confidential files. This information will not be accessible to anyone but the study investigators. Furthermore, all of the data (including MRI scans) will be stored behind firewalls at the New York State Psychiatric Institute. Finally, to ensure protection of confidentiality of the sensitive information that will be obtained in this project, I will apply for a Certificate of Confidentiality from NIH.

Clinical Issues Necessary referral during the course of the study will be made, if the need arises. On-site clinicians in this proposal (e.g., Drs. Posner, Simpson, or Rynn) will notify the treating clinician if abnormalities are found on the MRI.

Distress during the generalization experiment. All consent forms for the procedures that potentially induce distress will provide this information (e.g., the startle probe). We will conduct the generalization task immediately after an initial structural scan so that participants undergo an aversive procedure before their tolerance might run out. All participants will communicate directly with technologists and study staff that are

trained and have experience to perform MRI experiments in youth with psychiatric disorders. If they wish, participants can terminate the experiment immediately and the subject will be removed from the scanner.

**7. Risk/Benefit Ratio** Potential benefits to society are large in regard to improved understanding neural underpinnings of pathological anxiety specifically linked to heightened sensitivity to (potential) threat and its developmental changes. This knowledge in turn could lead to better interventions and prevention of the severe long-term consequences facing not only many youths but also adults with pathological anxiety. Youth and their parents will be informed of any clinically significant findings from the MRI. Each subject will receive payment for participating in the study. The risks of participating in this study are minimal, especially in relation to the potential benefits and public health importance of improved understanding of pathological anxiety.

## **INCLUSION OF WOMEN AND MINORITIES**

We will attempt to recruit equal numbers of females and males, consistent with the epidemiology of child and adolescent anxiety disorders and that of the New York metropolitan community, which is 52% female and 48% male. Efforts will be made to have the study population reflect the ethnic distribution of the area covered by the Columbia University Medical Campus and the New York State Psychiatric Institute. The recruitment of Hispanic participants will be consistent with the Hispanic population for the NY-013 congressional district (about 50% Hispanic). Our figures will be about 50% White and 50% Black or African Americans. Overall, NIH guidelines for the inclusion of females and minorities as subjects in clinical research will be followed. We will attempt to recruit equal numbers of each gender from each of the above racial groups. Previous neuroimaging studies in Dr. Posner laboratory achieved these gender, racial, and ethnic representations, and we foresee the same for this study. We will analyze demographic data every three months and if we are failing to achieve these marks, we will increase our recruitment of the under-represented group by extending recruitment to other area clinics that include the under-represented group. There will be no exclusion of subjects based on gender, race, or ethnicity.

## Planned Enrollment Report

**Study Title:** Identification of Neural Correlates of Fear Over-Generalization in Pathological Anxiety in Youth

**Domestic/Foreign:** Domestic

**Comments:** The estimates presented in this table are consistent with the recruitment profiles for previous studies in pediatric anxiety disorders and related populations at this site. In terms of gender, the recruitment goal is 50% male and 50% female. The Hispanic recruitment is consistent with the Hispanic population for the NY-013 congressional district (about 50% Hispanic). Our figures are about 50% White and 50% Black or African Americans.

Racial Categories	Ethnic Categories				Total	
	Not Hispanic or Latino		Hispanic or Latino			
	Female	Male	Female	Male		
American Indian/Alaska Native	0	0	0	0	0	
Asian	0	0	0	0	0	
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	
Black or African American	9	9	9	10	37	
White	10	9	9	10	38	
More than One Race	0	0	0	0	0	
<b>Total</b>	<b>19</b>	<b>18</b>	<b>18</b>	<b>20</b>	<b>75</b>	

Study 1 of 1

## INCLUSION OF CHILDREN

The basic study design is to assess fear generalization behavior and underlying neural circuitry in adolescents (ages 13-17 years old) across the spectrum of anxiety including both clinically anxious groups and subthreshold anxiety individuals. We will recruit three groups of youth (n=75): 25 healthy youth, 25 youth with subthreshold anxiety, and 25 youth with DSM-5 anxiety disorders.

The PI, Dr. Jiook Cha, the sponsor, Dr. Posner (who is a child psychiatrist and will provide clinical assessments), and the research assistants who will work directly with the children during this K award project have extensive experience conducting MRI experiments with children and adolescents.

Over the past 12 years, the Division of Child and Adolescent Psychiatry and the MRI Unit at the New York State Psychiatric Institute has acquired more than 1,000 MRI scans in children and adolescents, many of whom have had severe anxiety disorders, ADHD, movement disorders, and cognitive impairments. Drs. Cha and Posner's research team has extensive experience in the use of relaxation procedures and behavioral techniques to help children enjoy their experience in the scanner and to lay sufficiently still to provide motion-free images. Parents are allowed to accompany their child into the scanning suite. As already described in the research strategy, subjects will be offered the opportunity to undergo a desensitization procedure and relaxation training prior to having their MRI study (see 12. Research Strategy—C2.5. Experimental Procedures).

These procedures minimize potential anxiety the subjects may have concerning the MRI scan, and they help to acquire motion-free imaging. Drs. Cha and Posner will also train the research assistants in how to help children feel calm and prepared for the MRI, and how to help the children if they become uncomfortable or frustrated at any point during the visit. Both Drs. Cha and Posner will be available to the research assistants at all times that a study visit is taking place in case questions arise during a visit. The MRI Suite and the assessment offices in the Child Psychiatry Division are all extremely child friendly. The offices have age appropriate art on the walls, and the furniture is comfortable for child seating. The spaces are specifically designed to help children feel at ease and happy to participate.

Including 75 adolescents, this research proposal will provide crucial pilot data for a future larger-scale R01 application aimed at charting the developmental trajectories of the threat processing corticolimbic system across the developmental stages (from children to adults) and across the spectrum of anxiety (from normal to abnormal). Therefore, including children (ages 13-17 years old) in this proposal is essential to this purpose.