PI: **LEWIS, MARK H**	Title: Developing a novel treatment for restricted inflexible behavior	
Received: 07/16/2010	FOA: PA10-069	Council: 01/2011
Competition ID: ADOBE-FORMS-B	FOA Title: NIH Exploratory Developmental Research Grant Program (Parent R21)	
1 R21 MH091554-01A1	Dual:	Accession Number: 3317037
IPF: 513806	Organization: UNIVERSITY OF FLORIDA	
Former Number:	Department: Psychiatry	
IRG/SRG: CPDD	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 150,000 Year 2: 125,000	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Mark Lewis PhD	University of Florida	PD/PI
Soo-Jeong Kim MD	University of Florida	Faculty
Krestin Radonovich Ph.D	University of Florida	Faculty
Daniel Tucker MD	University of Florida	Faculty
Timothy Vollmer Ph.D	University of Florida	Faculty

OMB Number: 4040-0001
Expiration Date: 06/30/2011

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. * TYPE OF SUBMISSION
☐ Pre-application ☒ Application ☐ Changed/Corrected Application

2. DATE SUBMITTED | **Applicant Identifier**

4. a. Federal Identifier: MH091554

b. Agency Routing Identifier:

5. APPLICANT INFORMATION

*** Organizational DUNS:** 969663814

* Legal Name: University of Florida
Department: Sponsored Research
Division:
* Street1: 219 Grinter Hall
Street2: PO Box 115500
* City: Gainesville
County / Parish: Alachua
* State: FL: Florida
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 32611-5500

Person to be contacted on matters involving this application
Prefix: Dr.
* First Name: Thomas
Middle Name: E.
* Last Name: Walsh
Suffix: PhD
* Phone Number: 352-392-1582
Fax Number: 352-392-4400
Email: ufawards@ufl.edu

6. * EMPLOYER IDENTIFICATION *(EIN) or (TIN):* 59-6002052

7. * TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education
Other (Specify):
Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:
☐ New ☒ Resubmission
☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).
☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration
☐ E. Other (specify):

* Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. * NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:
TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
Developing a novel treatment for restricted inflexible behavior

12. PROPOSED PROJECT:
* Start Date: 04/01/2011
* Ending Date: 03/31/2013

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT:** FL-006

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION
Prefix: Dr.
* First Name: Mark
Middle Name: H.
* Last Name: Lewis
Suffix: PhD
Position/Title: Professor
* Organization Name: University of Florida
Department: Psychiatry
Division: Medicine
* Street1: 100 Newell Drive, L4-100
Street2: Box 100256
* City: Gainesville
County / Parish: Alachua
* State: FL: Florida
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 32611-0256
* Phone Number: 352-392-3681
Fax Number: 352-392-2579
* Email: marklewis@ufl.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	393,407.00
b. Total Non-Federal Funds	0.00
c. Total Federal & Non-Federal Funds	393,407.00
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 penalities. (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

Add Attachment | Delete Attachment | View Attachment

19. Authorized Representative

Prefix: Mr. * First Name: Brian Middle Name:

* Last Name: Prindle Suffix:

* Position/Title: Associate Director

* Organization: University of Florida

Department: Sponsored Research Division:

* Street1: 219 Grinter Hall

Street2: PO Box 115500

* City: Gainesville County / Parish: Alachua

* State: FL: Florida Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 32611-5500

* Phone Number: 352-392-1582 Fax Number: 352-392-4400

* Email: ufproposals@ufl.edu

*** Signature of Authorized Representative**: Brian Prindle

*** Date Signed**: 07/16/2010

20. Pre-application Add Attachment | Delete Attachment | View Attachment

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

OMB Number: 4040-0010
Expiration Date: 08/31/2011

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: University of Florida

DUNS Number: 9696638140000

* Street1: 219 Grinter Hall

Street2: PO Box 115500

* City: Gainesville County: Alachua

* State: FL: Florida

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: 32611-5500 * Project/ Performance Site Congressional District: FL-006

Project/Performance Site Location 1 ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:

DUNS Number:

* Street1:

Street2:

* City: County:

* State:

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: * Project/ Performance Site Congressional District:

Additional Location(s) Add Attachment Delete Attachment View Attachment

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ☒ Yes ☐ No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☒ No

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

If no, is the IRB review Pending? ☐ Yes ☒ No

IRB Approval Date: 02/03/2010

Human Subject Assurance Number: FWA0000579

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 on the environment? ☐ Yes ☒ No

4.b. If yes, please explain:

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

4.d. If yes, please explain:

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

5.a. If yes, please explain:

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

6.a. If yes, identify countries:

6.b. Optional Explanation:

7. * Project Summary/Abstract 1239-Project_Summary.pdf Add Attachment | Delete Attachment | View Attachment

8. * Project Narrative 1240-Project_Narrative.pdf Add Attachment | Delete Attachment | View Attachment

9. Bibliography & References Cited 1241-BIBLIOGRAPHY.pdf Add Attachment | Delete Attachment | View Attachment

10. Facilities & Other Resources 1242-Facilities.pdf Add Attachment | Delete Attachment | View Attachment

11. Equipment Add Attachment | Delete Attachment | View Attachment

12. Other Attachments Add Attachments | Delete Attachments | View Attachments

Project Summary/Abstract

Autism spectrum disorders (ASD) are defined, in part, by behavior that can be characterized as restricted and inflexible. Such behavior is exemplified by the so-called “higher order” restricted repetitive behaviors characterized by their insistence on sameness or resistance to change. Behaviors characterized in this way are pervasive in children with ASD and can significantly interfere with opportunities to develop functional behaviors and more complex repertoires. Thus, restricted, inflexible behavior likely adversely impacts brain and behavioral development, and intervention directed toward such behavior should have significant positive impact on neuroplasticity and neurodevelopmental trajectories. The overall goal of the proposed project is to initiate a program of research to develop a novel treatment approach to restricted, inflexible behavior, a clinically important and highly understudied problem in neurodevelopmental disorders in general and autism in specific. Rather than target a particular compulsive, restricted, or repetitive behavior for modification, our proposed strategy is to promote the development of flexibility and variability using age appropriate, functional activities. As such, the proposed project is highly translational as our approach to intervention is based on a body of animal and human laboratory studies that have established the empirical foundation for such an approach. Effective interventions are hypothesized to have generalizable effects on development and will be highly translatable to other neurodevelopmental disorders. Thus, we propose to assess restricted, inflexible behavior in children with ASD and typically developing controls and then pilot test an experiential intervention to determine if it will directly promote variable and flexible adaptive responding in children with ASD. This project is highly innovative in targeting flexibility and variability as goals of the intervention. No systematic efforts have been made to develop effective methods for the behavioral treatment of the general rigidity/inflexibility that is most characteristic of autism and common in related neurodevelopmental disorders. Finally, the proposed project represents a translational effort to take laboratory-based animal and human studies and apply them to a focused intervention directed at restricted, inflexible behavior that can ultimately be conducted in a community setting. If successful, the proposed treatment approach should have considerable potential for becoming a widely used, cost effective treatment approach.

Project Narrative

Autism spectrum disorders (ASD) are defined, in part, by behavior that can be characterized as restricted and inflexible. No systematic attempts have been made to develop effective methods for the behavioral/educational treatment of the higher-order ritualistic repetitive behaviors and general rigidity/inflexibility that are most characteristic of autism. Establishing assessment methods for restricted, inflexible behavior and interventions to increase variability and flexibility in responding will be of significant benefit to individuals with autism and their families.

Facilities & Other Resources

Clinical: The Department of Psychiatry will provide guidance and facilities for subject care, including screening tests and medical emergency handling. Subjects and controls will be seen at the Child Psychiatry Autism Clinic, located on the fourth floor of Shands hospital. The Autism Program provides complete and comprehensive assessment of children with Autism Spectrum Disorders. All ages between 12 months and 18 years are represented in this clinic and the clinic typically sees over 300 patients a year.

Resources will also be available through the University of Florida Center for Autism and Related Disorders (CARD). The University of Florida/Gainesville CARD provides services for families with an individual with an autistic-related, or pervasive developmental, disorder within the geographical region which includes Alachua, Bradford, Citrus, Columbia, Dixie, Gilchrist, Hamilton, Hernando, Lafayette, Levy, Marion, Putnam, Suwannee, and Union Counties. Currently, CARD serves approximately 300 individuals in Alachua County. Clinicians and staff at CARD will be available for subject referral and screening.

Computer: All offices at the University of Florida have the capability to run word processing and database programs (i.e. Word, Excel). These computers are also attached to a network system. Necessary computer support will be provided by the Department of Psychiatry.

Office: Dr. Lewis has an office and lab in the McKnight Brain Institute (MBI). Dr. Kim also has a lab in the MBI. Drs. Tucker, Kim, and Radonovich have offices in the office in the Human Development Building at the University of Florida. Dr. Vollmer has laboratory and office space for him and his students in the Department of Psychology. There is also administrative, secretarial and technical support at both the MBI and Psychology Department sites.

Other: The University of Florida is a major research center, as evidenced by the depth and experience of its research faculty. UF provides a rich academic environment in which established research scientists are available resources for consultation in a number of disciplines. With the addition of the McKnight Brain Institute, the level of support and enrichment has been dramatically increased.

The University of Florida Health Science Center has expanded since 1956 into the most comprehensive academic health center in the Southeast. The “center” now encompasses 6 colleges, a statewide network of affiliated hospitals and clinics, including Shands Hospital as the flagship teaching hospital, and the neighboring Veterans Affairs Medical Center of Gainesville.

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. * First Name: Mark Middle Name: H.
* Last Name: Lewis Suffix: PhD
Position/Title: Professor Department: Psychiatry
Organization Name: University of Florida Division: Medicine
* Street1: 100 Newell Drive, L4-100
Street2: Box 100256
* City: Gainesville County/ Parish: Alachua
* State: FL: Florida Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 32611-0256
* Phone Number: 352-392-3681 Fax Number: 352-392-2579
* E-Mail: marklewis@ufl.edu

Credential, e.g., agency login: mhlewis

*** Project Role:** PD/PI **Other Project Role Category:**

Degree Type: PhD
Degree Year: 1980

***Attach Biographical Sketch** 1234-Lewis_Biosketch.pdf [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

PROFILE - Senior/Key Person 1

Prefix: Dr. * First Name: Soo-Jeong Middle Name:
* Last Name: Kim Suffix: MD
Position/Title: Assistant Professor Department: Psychiatry
Organization Name: University of Florida Division: Medicine
* Street1: 100 Newell Drive, L4-100
Street2: Box 100256
* City: Gainesville County/ Parish: Alachua
* State: FL: Florida Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 32611-0256
* Phone Number: 352-392-3681 Fax Number:
* E-Mail: soojkim@ufl.edu

Credential, e.g., agency login:

*** Project Role:** Faculty **Other Project Role Category:**

Degree Type: MD
Degree Year: 1993

***Attach Biographical Sketch** 1235-KIM_BIOSKETCH.pdf [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 2

Prefix: Dr. * First Name: Krestin Middle Name:
* Last Name: Radonovich Suffix: Ph.D
Position/Title: Assistant Professor Department: Psychiatry
Organization Name: University of Florida Division: Medicine
* Street1: 100 Newell Drive, L4-100
Street2: Box 100256
* City: Gainesville County/ Parish: Alachua
* State: FL: Florida Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 32611-0256
* Phone Number: 352-392-3681 Fax Number:
* E-Mail: kradonov@ufl.edu

Credential, e.g., agency login:

*** Project Role:** Faculty **Other Project Role Category:**

Degree Type: PhD
Degree Year: 2001

***Attach Biographical Sketch** 1236-Radonovich_Biosketch_070 Add Attachment Delete Attachment View Attachment
Attach Current & Pending Support Add Attachment Delete Attachment View Attachment

PROFILE - Senior/Key Person 3

Prefix: Dr. * First Name: Daniel Middle Name: M.
* Last Name: Tucker Suffix: MD
Position/Title: Associate Professor Department: Psychiatry
Organization Name: University of Florida Division: Medicine
* Street1: 100 Newell Drive, L4-100
Street2: Box 100256
* City: Gainesville County/ Parish: Alachua
* State: FL: Florida Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 32611-0256
* Phone Number: 352-392-3681 Fax Number:
* E-Mail: dantucker@ufl.edu

Credential, e.g., agency login:

*** Project Role:** Faculty **Other Project Role Category:**

Degree Type: MD
Degree Year: 1975

***Attach Biographical Sketch** 1237-Tucker_Biosketch.pdf Add Attachment Delete Attachment View Attachment
Attach Current & Pending Support Add Attachment Delete Attachment View Attachment

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 4

Prefix: Dr. * First Name: Timothy Middle Name:

* Last Name: Vollmer Suffix: Ph.D

Position/Title: Professor Department: Psychology

Organization Name: University of Florida Division: Liberal Arts & Sciences

* Street1: PO Box 112250

Street2:

* City: Gainesville County/ Parish: Alachua

* State: FL: Florida Province:

* Country: USA: UNITED STATES * Zip / Postal Code: 32611-2250

* Phone Number: 352-392-0601 x280 Fax Number: 352-392-7985

* E-Mail: vollmera@ufl.edu

Credential, e.g., agency login:

*** Project Role:** Faculty **Other Project Role Category:**

Degree Type: PhD

Degree Year: 1992

***Attach Biographical Sketch**	1238-Vollmer_Biosketch.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

Tracking Number:GRANT10655481 Funding Opportunity Number:PA-10-069 Received Date:2010-07-16T09:31:46-04:00

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Mark H. Lewis, Ph.D.	Professor
eRA COMMONS USER NAME mhlewis	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Bowdoin College, Brunswick, ME	B.A.	1972	Psychology
Western Michigan University, Kalamazoo, MI	M.A.	1975	Psychology
Vanderbilt University, Nashville TN	Ph.D.	1980	Psychology
University of North Carolina, Chapel Hill, NC	Post-Doc	1980-83	Neuropharmacology

A. Personal Statement

I have been focused on restricted, inflexible behavior, broadly construed, for much of my career. This work has included studies of repetitive behavior in individuals with autism and intellectual and developmental disability as well as work in animal models. I have been involved in treatment studies of repetitive behavior involving individuals with neurodevelopmental disorders and my basic laboratory studies are translational in nature, including development of potential pharmacological treatment approaches. The proposed project relies on laboratory findings from both animal and human subjects. In addition, our animal work has shown the robust effects on repetitive behavior of providing animals with opportunities for more varied and flexible responding. Finally, the collaboration with Dr. Vollmer provides an exciting opportunity to combine our experience and expertise and pursue a treatment strategy based on principles of the experimental analysis of behavior.

B. Positions and Honors.

Positions and Employment

1972-1974 Staff psychologist, Director of Staff Training, Mental Retardation Division; Central State Hospital, Milledgeville, GA
1975-1977 Staff psychologist, Director of Staff Training, Mental Retardation Division; Central State Hospital, Milledgeville, GA
1977-1978 Research Assistant, Vanderbilt University/Peabody College, Nashville, TN
1978-1980 Pre-doctoral Fellow, Peabody College/Vanderbilt University, Nashville, TN
1980-1982 Post-doctoral Fellow, Brain and Development Research Center, University of North Carolina School of Medicine, Chapel Hill, NC
1982-1983 Research Associate, Brain and Development Research Center, University of North Carolina School of Medicine, Chapel Hill, NC
1983-1986 Assistant Professor of Psychiatry, University of Medicine & Dentistry of New Jersey-SOM, Camden, NJ
1986-1989 Research Assistant Professor of Psychiatry; Research Scientist, Brain and Development Research Center, University of North Carolina, Chapel Hill, NC
1989-1992 Associate Professor, Dept. of Psychiatry; Research Scientist, Brain and Development Research Center, Univ. of North Carolina, Chapel Hill, NC
1992-1995 Associate Professor of Psychiatry, Neuroscience, and Psychology, University of Florida, Gainesville, FL.
1995-Present Professor of Psychiatry, Neuroscience, and Psychology, University of Florida, Gainesville, FL.
2003-2007 Associate Chair for Research, Department of Psychiatry, University of Florida
2006-Present Executive Director, Center for Autism and Related Disabilities (CARD) Program, University of Florida

Other Experience and Professional Memberships

Member, Editorial Board, Journal of Mental Health Research in Intellectual Disabilities (JMHRID)
Member, UNC Neurodevelopmental Disorders Reseach Center Scientific Advisory Board

Member, Executive Committee, Gatlinburg Conference on Research in Mental Retardation and Developmental Disabilities (1997-2009)
Consulting Editor, American Journal on Intellectual and Developmental Disabilities
Executive Director, University of Florida Center for Autism and Related Disorders (CARD)

Awards/Honors

B.A. magna cum laude, Departmental Honors in Psychology
Educational Stipend Award, Georgia Department of Human Resources
Departmental Honors in Psychology, Western Michigan University
NICHD Pre-doctoral Fellowship
NICHD Post-doctoral Fellowship; New Jersey Governor's Council on Prevention of Mental Retardation.

C. Selected peer-reviewed publications (in chronological order).

Gendreau PL, Petitto JM, Schnauss R, Frantz KJ, Van Hartesveldt C, Gariepy J-L, Lewis MH (1997) Effects of the D3 dopamine receptor antagonist U9919a on emotional reactivity and motor behavior in C57BL/6 mice. European J Pharmacology, 337:147-155.

Gariépy J-L, Gendreau PL, Cairns RB, Lewis MH (1998) D_1 dopamine receptors and the reversal of isolation-induced behaviors in mice. Behavioural Brain Research 95: 103-111.

McNamara RK, Stumpo DJ, Morel LM, Lewis MH, Wakeland EK, Blackshear PJ, Lenox RH (1998) Effect of reduced myristoylated alanine-rich C kinase substrate expression on hippocampal mossy fiber development and spatial learning in mutant mice: Transgenic rescue and interactions with gene background. Proceedings of the National Academy of Science USA 95: 14517-14522, 1998.

Gendreau PL, Pettito JM, Gariépy J-L, Lewis MH (1998) D_2-like dopamine receptor mediation of social-emotional reactivity in a mouse model of anxiety: strain and experience effects. Neuropsychopharmacology 18: 210-221.

Lewis MH, Bodfish JW (1998) Repetitive behavior in autism. Mental Retardation and Developmental Disabilities Research Review, 4: 80-89.

Powell SB, Newman HA, Pendergast J, Lewis MH (1999) A rodent model of spontaneous stereotypy: initial characterization of developmental, environmental, and neurobiological factors. Physiology & Behavior, 66(2):355-363.

Petitto JM, Gariepy JL, Gendreau PL, Rodriguiz R, Lewis MH, Lysle DT (1999) Differences in NK cell function in mice bred for high and low agression: Genetic linkage between complex behavioral and immunological traits? Brain, Behavior, and Immunity, 13: 175-186.

Klein RL, Lewis MH, Muzyczka N, Meyer EM (1999) Prevention of 6-hydroxydopamine-induced rotational behavior by BDNF somatic gene transfer. Brain Research 847: 314-320.

Lewis MH, Gluck JP, Petitto JM, Hensley LL, Ozer H (2000) Early social deprivation in non-human primates: long term effects on survival and cell-mediated immunity. Biological Psychiatry 47:119-26.

Powell SB, Newman HA, McDonald TA, Bugenhagen P, Lewis MH (2000). Development of spontaneous stereotypy in deer mice: effects of early and late exposure to a more complex environment. Developmental Psychobiology, 37, 100-108.

Gendreau PL, Petitto JM, Petrova A, Gariépy J-L, Lewis MH (2000) D3 and D2 dopamine receptor agonists differentially modulate isolation-induced social-emotional reactivity in mice Behavioral Brain Research 114: 107-117.

Bodfish JW, Symons FJ, Parker DE, Lewis MH (2000) Varieties of repetitive behavior in autism: comparisons to mental retardation. Journal of Autism and Developmental Disorders 30: 237-243.

Bodfish JW, Parker DE, Lewis MH, Sprague RL, Newell KM (2001) Stereotypy and Motor Control: Differences in postural stability dynamics of persons with stereotyped and dyskinetic movement disorders. American Journal on Mental Retardation 106: 123-134.

Turner CA, Presti MF, Newman HA, Bugenhagen P, Crnic L, Lewis MH (2001) Spontaneous stereotypy in an animal model of Down Syndrome: Ts65Dn Mice. Behavior Genetics 31(4): 393-400.

Presti MF, Powell SB, Lewis MH (2002) Dissociation between spontaneously emitted and apomorphine-induced stereotypy in Peromyscus maniculatus bairdii Physiol Behav, 75 (3): 347-353.

Turner CA, Yang MC, Lewis MH (2002) Environmental enrichment: effects on stereotyped behavior and regional neuronal metabolic activity Brain Res, 938 (1-2): 15-21.

Presti MF, Mikes HM, Lewis MH (2003). Selective blockade of spontaneous motor stereotypy via intrastriatal pharmacological manipulation. Pharmacology, Biochemistry, & Behavior, 74:833-839.

Turner CA, King MA, Lewis MH (2003) Environmental enrichment: effects on stereotyped behavior and dendritic morphology. Developmental Psychobiology, 43:20-27.
Turner CA, Lewis MH (2003) Environmental enrichment: effects on stereotyped behavior and neurotrophin levels. Physiology & Behavior, 80:259-66.
Murphy TK, Sajid M, Soto O, Shapira N, Edge P, Yang M, Lewis MH, Goodman WK (2003). Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. Biological Psychiatry, 55:61-68
Presti MF, Gibney BC, Lewis MH (2004) Effects of intrastriatal administration of selective dopaminergic ligands on spontaneous stereotypy in mice. Physiology & Behavior, 80:433-439.
Presti MF, Watson CJ, Kennedy RT, Yang M, Lewis MH (2004) Behavior related alterations of striatal neurochemistry in a mouse model of stereotyped movement disorder. Pharmacology, Biochemistry & Behavior, 77(3):501-7.
Shapira NA, Lessig MC, Lewis MH, Goodman WK, Driscoll DJ. (2004) Effects of topiramate in adults with Prader-Willi syndrome. Am J Ment Retard, 109(4):301-9.
Lewis MH (2004) Environmental complexity and central nervous system development and function. Ment Retard Dev Disabil Res Rev. 10(2):91-5.
Presti MF, Lewis MH (2005) Striatal opioid peptide content in an animal model of spontaneous stereotypic behavior. Behav Brain Res. 57(2):363-8.
Lewis, M.H., Lazoritz, M. (2005). Psychopharmacology of Autism Spectrum Disorders. *Psychiatric Times*, 22(6), online exclusive (http://www.psychiatrictimes.com/ showArticle.jhtml?articleId=164303316).
Hadley C, Hadley B, Ephraim S, Yang M, Lewis, MH. (2006) Spontaneous stereotypy and environmental enrichment in deer mice (*Peromyscus maniculants*): Reversibility of experience. *Applied Animal Behaviour Science,* 97:312-322.
Lewis MH, Tanimura Y, Lee LW, Bodfish JW. (2007) Animal models of restricted repetitive behavior in autism. *Behavioural Brain Research,* 10;176(1):66-74.
Storch EA, Merlo LJ, Bengtson M, Murphy TK, Lewis MH, Yang MC, Jacob ML, Larson M, Hirsh A, Fernandez M, Geffken GR, Goodman WK. (2007) D-Cycloserine Does Not Enhance Exposure-Response Prevention Therapy in Obsessive-Compulsive Disorder. *Intern'l J Clin Psychopharm*, 22(4):230-237.
Tanimura Y, Yang MC, Lewis MH. (2008) Procedural learning and cognitive flexibility in a mouse model of restricted, repetitive behaviour. *Behav Brain Res*, 189(2):250-6.
Lewis, MH, Kim SJ. (2009) The pathophysiology of restricted repetitive behavior. J Neurodevelop Disord, 1:114–132.
Huang Z, Dauer DJ, Ha GK, Lewis MH, Petitto JM. (2009) Interleukin-2 deficiency-induced T cell autoimmunity in the mouse brain. Neurosci Lett. 29;463(1):44-8.
Tanimura Y, Ogoegbunam FC, Lewis MH. (2009) Amphetamine-induced sensitization and spontaneous stereotypy in deer mice. Pharmacol Biochem Behav. 92(4):670-5.
Pawlowicz A, Demner A, Lewis MH. (2010). Effects of access to voluntary wheel running on the development of stereotypy. Behav Processes, 83(3):242-6
Tanimura Y, Vaziri S, Lewis MH. (2010). Indirect basal ganglia pathway mediation of repetitive behavior: Attenuation by adenosine receptor agonists. Behavioural Brain Research, 210, 116-122.
Lee MH, Bodfish JW, Lewis MH, Newell KM. (2010). Low dimensional temporal organization of spontaneous eye blinks in adults with developmental disabilities and stereotyped movement disorder. Research in Developmental Disabilities, 31(1), 250-255.
Tanimura Y, Yang MCK, Ottens AK, Lewis MH. (In press). Development and temporal organization of repetitive behavior in an animal model. Developmental Psychobiology.
Fournier KA, Kimberg CI, Radonovich KJ, Tillman MD, Chow JW, Lewis MH, Bodfish JW, Hass CJ. (In press). Increased static and dynamic postural control in children with autism spectrum disorders. Gait and Posture.

D. Research Support.

Ongoing

Title: Fathers As In-Home Trainers of Autistic Children
Principal Investigator: J. Elder
Agency: NIH/NINR
Type: R01 Grant
Funding Period: 8/19/05-5/31/10

Specific aims of this proposal are: (a) to evaluate the effects of the expanded father training on skill acquisition by fathers, (b) to evaluate the effects of the expanded father training on skill acquisition by mothers,

(c) to evaluate the effects of the expanded in-home training on parental stress and family cohesion, and (d) to develop a Web based investigator-father feedback system and evaluate its feasibility during the training protocol and maintenance phases with a subset of five families.

Title: Restricted repetitive behaviors in autism
Principal Investigator: Mark H. Lewis, Ph.D.
Agency: Autism Speaks
Type: Pre-Doctoral Fellowship
Funding Period: 07/01/06-06/30/10

The current study proposes to use this model of restricted, repetitive behavior to determine how specific types of stereotyped behavior relate to particular components of motor control and cognitive flexibility.

Title: The Genetics of Restricted, Repetitive Behavior: An Inbred Mouse Model
Principal Investigator: Mark H. Lewis, Ph.D.
Agency: Autism Speaks
Type: Pilot Study Grant
Funding Period: 07/01/08-06/30/10

Using an F2 population generated from a cross of C58/J and C57BL/6J, we will conduct quantitative trait loci mapping to identify chromosomal loci associated with repetitive motor behavior as well as restricted behavior and resistance to change.

Title: Development of Persistent Repetitive Behavior in Animals
Principal Investigator: Mark H. Lewis, Ph.D.
Agency: NIH/NIMH
Type: R01 Grant
Funding Period: 05/01/09-04/30/11

The overall goal of this project will be to examine the development of repetitive motor behavior in a mouse model and identify the neurobiological mechanisms mediating the emergence and expression of habitual, persistent and inflexible motor behavior.

<u>Completed</u>
Title: Restricted Repetitive Behavior in Autism
Principal Investigator: Mark H. Lewis, Ph.D.
Agency: Riddle Institute
Type: R01 subcontract from NIMH
Funding Period: 7/13/04-4/30/08

The primary purpose of the proposed study is to compare children with autism to two comparison groups – a nonspecific developmental disability group and a typically developing children group - on a set of repetitive behavior measures. In addition the AUT and DD groups will be compared on neuromotor function tests and neurocognitive function tests.

Title: Stereotypies and Mental Retardation: Neurobiological Basis
Principal Investigator: Mark H. Lewis, Ph.D.
Agency: NICHD
Type: R01 HD30615-06
Funding Period 9/92 - 8/07

The overall goal of this project remains the elucidation of neurobiological bases of stereotyped and related repetitive behavioral disorders (i.e., compulsions, self injury), and the subsequent development of rational, safe and effective pharmacological treatments.

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Soo-Jeong Kim, MD	Assistant Professor
eRA COMMONS USER NAME SOOJKIM	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Year(s)	FIELD OF STUDY
Seoul National University College of Medicine, Seoul, South Korea	M.D.	1989-1993	Medicine
Seoul National University Hospital, Seoul, South Korea	Resident	1993-1998	Psychiatry
Seoul National University College of Medicine, Seoul, South Korea	M.Sc.	1997-1999	Psychiatry
University of Chicago, Chicago, Illinois	Resident	2001-2004	Psychiatry
University of Chicago, Chicago, Illinois	Fellow	2004-2005	Child & Adolescent Psychiatry
University of Illinois at Chicago, Illinois	Fellow	2005-2006	Child & Adolescent Psychiatry
University of Florida, Gainesville, Florida	M.Sc.	2007-2010	Medicine

A. Personal Statement

The overall goal of the proposed project is to initiate a research program to develop a novel treatment approach to restricted, inflexible behavior. Specifically, the proposed exploratory project will assess restricted, inflexible behavior in children with autism spectrum disorders (ASDs) and then test an intervention designed to promote variability and flexibility in a variety of adaptive responses. I am a board certified child psychiatrist and have special clinical and research interest in ASDs. As a clinician, I direct the ASD Specialty Clinic at the University of Florida Shands Medical Plaza. In my clinic, I have witnessed and experienced a great deal of frustration when children exhibit high levels of restricted, inflexible behavior that does not respond to existing treatment modalities. Therefore, there is a sense of urgency when it comes to find a different, novel treatment approach to the restricted, inflexible behavior. As a researcher, I am focused to study the genetic underpinnings of restricted repetitive behavior, for which I have obtained the NIMH K23 and R03 awards. My role in the proposed research includes the recruitment of potential participants, ascertainment of ASDs and assessment of specific restricted, inflexible behavior characterized by their insistence on sameness or resistance to change. In summary, the current application builds on the collective expertise of the PI and co-investigators. As a co-investigator, my expertise and experience in ASD research will help the PI successfully carry out the proposed research program.

B. Positions and Honors

Positions and Employment

1999-2001 Research Associate, Department of Psychiatry, University of Chicago, Chicago, IL
2006- Assistant Professor, Department of Psychiatry, University of Florida College of Medicine, Gainesville, FL
2010- Joint Assistant Professor of Pediatrics, University of Florida, Gainesville, FL

Professional Memberships

2004- Member, American Psychiatric Association (APA)
2005- Member, American Academy of Child and Adolescent Psychiatry (AACAP)
2005- Member, American Medical Association (AMA)

Honors

2000 Daniel X. Freedman’s Fellowship: Department of Psychiatry, University of Chicago
2001 Chairman's award; Department of Psychiatry, University of Chicago

2003	IMG Mentorship Program Fellowship: American Association of Directors of Psychiatric Residency Training (AADPRT)
2005	APA/Lilly Research Award: American Psychiatric Association (APA)
2007	NARSAD Young Investigator's Award

Certification and Licensure

1993	Korean Medical license (Physician)
1998	General Psychiatry Board certification in Korea
2003	State of Illinois License (Physician)
2006	ABPN Board certification (Psychiatry)
2006	State of Florida License (Medical doctor)
2007	ABPN Board certification (Child and Adolescent Psychiatry)

C. Selected peer-reviewed publications (Selected from 26 peer-reviewed publications)

1. **Kim SJ**, Cook EH Jr. (2000) Novel de novo nonsense mutation of MeCP2 in a patient with Rett syndrome. *Human Mutation,* 15(4): 382-383.
2. **Kim SJ**, Veenstra-VanderWeele J, Hanna GL, Gonen D, Leventhal BL, Cook EH Jr. (2000) Mutation screening of human 5-HT_{2B} receptor gene in early-onset obsessive-compulsive disorder. *Mol Cell Probes,* 14(1): 47-52.
3. Veenstra-VanderWeele J, **Kim SJ**, Gonen D, Hanna GL, Leventhal BL, Cook EH Jr. (2001) Genomic Organization of the *SLC1A1*/EAAC1 Gene and Mutation Screening in Early-Onset Obsessive-Compulsive Disorder. *Mol Psychiatry*, **6:** 160-167.
4. Herzing LB, **Kim SJ**, Cook EH Jr, Ledbetter DH. (2001) The human aminophospholipid-transporting ATPase gene ATP10C maps adjacent to UBE3A and exhibits similar imprinted expression. *Am J Hum Genet,* 68**:** 1501-1505.
5. **Kim SJ**, Herzing LB, Veenstra-VanderWeele J, Lord C, Courchesne R, Leventhal BL, Ledbetter DH, Courchesne E, Cook EH Jr. (2002) Mutation screening and transmission disequilibrium study of ATP10C in autism. *Am J Med Genet,* 114(2):137-143.
6. Veenstra-VanderWeele J, **Kim SJ**, Lord C, Courchesne R, Akshoomoff N, Leventhal BL, Courchesne E, Cook EH Jr. (2002) Transmission disequilibrium studies of the serotonin 5-HT_{2A} receptor gene (HTR2A) in autism. *Am J Med Genet,* 114(3): 277-283.
7. **Kim SJ**, Cox N, Courchesne R, Lord C, Corsello C, Akshoomoff N, Guter S, Leventhal BL, Courchesne E, Cook EH Jr. (2002) Transmission disequilibrium mapping at the serotonin transporter gene (SLC6A4) region in autistic disorder. *Mol Psychiatry,* 7: 278–288.
8. **Kim SJ**, Young LJ, Gonen D, Veenstra-VanderWeele J, Courchesne R, Courchesne E, Lord C, Leventhal BL, Cook EH Jr, Insel TR. (2002) Transmission disequilibrium testing of arginine vasopressin receptor 1A *(AVPR1*A) polymorphisms in autism. *Mo. Psychiatry*, 7: 503-507.
9. **Kim SJ**, Badner J, Cheon KA, Kim BN, Yoo HJ, Kim SeJ, Cook E Jr, Leventhal BL, Kim YS. (2005) Family-based association study of the serotonin transporter gene polymorphisms in Korean ADHD trios. *Am. J. Med. Genet. B. Neuropsychiatr Genet.* 139(1):14-18.
10. Brune CW, **Kim SJ**, Salt J, Leventhal BL, Lord C, Cook EH Jr. (2006) 5-HTTLPR Genotype-specific Phenotype in Children and Adolescents with Autism. *Am J Psych*, 163(12):2148-56.
11. Cross S, **Kim SJ**, Weiss LA, Delahanty RJ, Sutcliffe JS, Leventhal BL, Cook EH Jr, Veenstra-Vanderweele J. (2008) Molecular Genetics of the Platelet Serotonin System in First-Degree Relatives of Patients with Autism. *Neuropsychopharmacology*, 33(2):353-60.
12. **Kim SJ**, Brune CW, Kistner EO, Christian SL, Courchesne EH, Cox NJ, Cook EH Jr. (2008) Transmission disequilibrium testing of the chromosome 15q11-q13 region in autism. *Am Med Genet B Neuropsychiatr Genet.*, 147B(7):1116-25.
13. Brune CW, **Kim SJ**, Hanna GL, Courchesne EH, Lord C, Leventhal BL, Cook EH Jr. (2008) Family-based association testing of OCD associated SNPs of SLC1A1 in an autism sample. *Autism Research,* 1:2: 108-113.
14. Lewis, MH, **Kim SJ.** (2009) The pathophysiology of restricted repetitive behavior. *J Neurodevelop Disord,* 1:2:114-132.
15. Suma Jacob, Camille W. Brune, Judith A. Badner, Katherine Ernstrom, Eric Courchesne, Catherine Lord, Bennett L. Leventhal, Edwin H. Cook, **Soo-Jeong Kim** (2010). Family-based association testing of glutamate transporter genes in autism. *Psychiatric Genetics (in press)*

D. Research Support

Ongoing Research Support

NARSAD 2007 Young Investigator Award Kim (PI) 07/01/2007-09/30/2010

Glutamate transporter genes and susceptibility to repetitive and stereotyped behavior and interests in autism spectrum disorders

The primary goal of this study is to investigate four glutamate transporter genes (*SLC1A1, SLC1A2, SLC1A3,* and *SLC1A6*) as positional and functional candidates for autism susceptibility, and to examine if these genes confer increased risk for repetitive and stereotyped behavior and interests in autism spectrum disorders (ASD).
Role: PI

PWSA (USA) 2008 Research Award Kim (PI) 08/01/2008 to 07/31/2011

Genetic Underpinnings of Restricted Repetitive Behavior (RRB)

The primary goal of this study is to test our hypotheses that specific genetic variants in the 15q11-q13 region contribute to the risk of specific forms of RRB, and that interactions between genes within the 15q11-q13 region and the 5-HT system genes would increase the susceptibility to specific forms of RRB in individuals with Prader-Willi syndrome (PWS).
Role: PI

R03 MH083673-02 Kim (PI) 09/01/2008 to 08/31/2011

Genetic study of Restricted Repetitive Behavior in Autism Spectrum Disorders

The primary goal of this study is to test our hypotheses that specific genetic variants in the GABA and glutamate system related genes contribute to the risk of specific forms of RRB, and that interactions between genes in these two neurotransmitter systems.
Role: PI

K23 MH082883-02 Kim (PI) 01/01/09 to 12/31/2012

Genetic Dissection of Restricted Repetitive Behavior

The primary goal of this study is to identify common genetic variants contributing to RRB among individuals with PWS and children with Autism Spectrum Disorders.
Role: PI

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Krestin J. Radonovich, PhD	Clinical Assistant Professor
eRA COMMONS USER NAME	
KRADONOV	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Minnesota-Duluth, Duluth, MN		1986-1988	Biology
University of North Dakota, Grand Forks, ND	B.S.	1991	Psychology
North Dakota State University, Fargo, ND	M.S.	1995	Clinical Psychology
University of Florida, Gainesville, FL	Ph.D.	2001	Clinical Pychology/Neuro-Psychology track
Johns Hopkins School of Medicine, Baltimore, MD	Post-doc	2001-2003	Neuropsychology

A. Personal Statement

The goal of my research is to investigate neuromotor functioning in children with autism. Specifically, I seek to characterize patterns of motor and cognitive performance based on models of neurological functioning. In this project it is our goal to target restricted, inflexible behavior in autism that likely adversely impacts brain and behavioral development. The overall goal of the proposed project is to initiate a program of research to develop a novel treatment approach to restricted, inflexible behavior, a clinically important and highly understudied problem in neurodevelopmental disorders. This project is highly translational as our approach to intervention is based on a body of animal and human laboratory studies that have established the empirical foundation for such an approach. My background and interests provide me with a unique combination of expertise in early childhood development, neuropsychology, and technical assessment that I can bring to this multidisciplinary project. I have successfully administered funded projects and collaborated with researchers from a variety of fields. My previous findings have demonstrated impaired postural control and gait patterns in children with autism spectrum disorder from ages 3-18. We have begun to publish peer-reviewed publications from these projects. In the current proposal, I will lend my clinical expertise to the project and be directly involved with all aspects of subject assessment and evaluation. It is my goal in my practice to use objective measures of functioning to better inform clinical practice in the diagnosis and treatment of autism. I remain committed to the seamless practice of integrating clinical-research in a medical academic training environment.

B. Positions and Honors

Professional Experience.

7/91-11/91	Program Counselor, Development Homes, Inc., Grand Forks, ND
1993-1994	Graduate Research Assistant, Department of Psychology, North Dakota State University.
1993-1994	Graduate Research Assistant, MeritCare Clinic Neuroscience, Fargo, ND.
1995-1997	Clinical Research Counselor, University of Vermont-Substance Abuse Treatment Center
1998-2000	School Liaison, University of Florida ADHD Program
1998-2000	Graduate Therapist, Children's Mental Health Unit for Autistic Disorders, University of Florida
2000-2001	Clinical Psychology Intern, Kennedy Krieger Institute/Johns Hopkins
2001-2003	Post-doctoral Fellow, Child & Adolescent Psychiatry, Johns Hopkins School of Medicine
2003-2004	Clinical Assistant Professor, Department of Pediatrics, University of Maryland School of Medicine
2007- 2008	Clinical Assistant Professor, Department of Clinical and Health Psychology, University of Florida College of Public Health and Health Professions
2004 - 2009-	Clinical Assistant Professor, Department of Psychiatry, University of Florida College of Medicine Adjunct Clinical Assistant Professor, Department of Neurology, University of Florida College of Medicine

Honors and Awards

1990	Psi Chi National Honor Society for Psychology, University of North Dakota
1992	North Dakota State University Graduate Research Council Fellowship
1993	Pi Kappa Phi National Honor Society, North Dakota State University.
1997	Dean's Scholarship, University of Florida College of Health Professions
2000	Young Investigators Award, NIH conference on Biological and Social Determinants of Child Development. Houston, TX.

C. Selected peer-reviewed publications (in chronological order)

McCourt ME, Mark VW, Radonovich KJ, Willison SK, Freeman P. (1997). The effects of gender, menstrual phase and practice on the perceived location of the midsagittal plane. Neuropsychologia, 35:717-724.

Budney AJ, Radonovich KJ, Higgins ST, Wong CJ. (1998). Adults seeking treatment for marijuana dependence: A comparison with cocaine-dependent treatment seekers. Experimental and Clinical Psychopharmacology, 6:419-426.

Crosson B, Radonovich K, Sadek JR, Gokcay D, Bauer RM, Fischler IS, Cato MA, Maron L, Auerbach EJ, Browd SR, Briggs RW. (1999). Accessing knowledge of emotional connotation in the left hemisphere during word generation. NeuroReport, 10:2449-2455.

Budney AJ, Higgins ST, Radonovich KJ, Novey PL. (2000). Abstinence-based vouchers increase marijuana abstinence during outpatient treatment for marijuana dependence. J Consult Clin Psych, 68:1051-1061.

Radonovich KJ, Mostofsky SH. (2004). Duration judgments in children with ADHD suggest deficient utilization of temporal information rather than general impairment in timing. Child Neuropsychology, 10:162-172.

Pulsifer M, Radonovich K, Belcher H, Butz A. (2004). Intelligence and school readiness in preschool children with prenatal drug exposure. Child Neuropsychology, 10:89-101

Dichter GS, Radonovich KJ, Turner-Brown LM, Lam KSL, Holtzclaw T, & Bodfish JW. (2010). Performance of children with autism spectrum disorders on the dimension-change card sort task. Journal of Autism and Developmental Disabilities, 448-456.

Fournier, K.A., Kimberg, C.I., Radonovich, K.J., Tillman, M.D., Chow, J.W., Lewis, M.H., Bodfish, J.W., & Hass, C.J. (2010; in press). Decreased static and dynamic postural control in children with autism spectrum disorders. Gait & Posture.

D. Research Support

Ongoing

Title: Abnormal Vestibulo-Ocular Reflexes in Autism: A Potential Endophenotype
Principal Investigator: Keith D. White, Ph.D.
Principal Investigator: Krestin J. Radonovich, Ph.D.
Type: Department of Defense Autism Idea Award. AR093169
Funding Period: 5/1/10-4/30/13

Completed

Title: Motor control in young children with autism
Principal Investigator: Chris J. Hass, Ph.D.
Co-Investigator: Krestin J. Radonovich, Ph.D.
Type: Autism Speaks Research Award
Funding Period : 7/1/07-6/30/09

Title: Restricted Repetitive Behavior in Autism
Principal Investigator: Mark H. Lewis, Ph.D.
Agency: Riddle Institute
Type: R01 subcontract from NIMH
Funding Period: 7/13/04-4/30/08

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Daniel M. Tucker, MD	Associate Professor
eRA COMMONS USER NAME	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Yale University, New Haven, CT	B.A.	1969	History
University of Florida College of Medicine, Gainesville, FL	M.D.	1975	
University of Florida College of Medicine, Gainesville, FL	Post-Doc	1975	Neuropathology
University of Louisville, KY	Resident	1975-78	Psychiatry
University of Louisville, KY	Fellow	1977-79	Child Psychiatry
Yale Child Study Center, New Haven, CT	Post-Doc	1994-1996	Child Psychiatry

A. Personal Statement

As a clinician in Child Psychiatry I have toiled in the care of youths and adults affected by autism, lamenting the lack of impact of available treatments. I directed a program of 40 in-patient beds for autistic young people, reflected upon the shortcomings of medication management, and kept open to the promise of other methods for helping reduce morbidities in this disorder by behavioral methods. I will contribute expertise in the diagnosis of autism for participants in this study and contribute enthusiasm for illuminating some alternative pathways toward effective treatment.

B. Positions and Honors.

Positions and Employment

1979-1993 Private Practice of Child and Adult Psychiatry, Louisville, Kentucky
1988-1993 Clinical Director, Children's Treatment Program; Founding Director, Child and Adolescent Partial Hospitalization Program; Our Lady of Peace Hospital, Louisville, KY
1993-1994 Medical Director, Rivendell Psychiatric Hospital, Panama City, FL
1995-1996 Medical Director, Gilead Community Services, Middletown, CT
1996-1997 Director, Children's Psychiatric In-patient Services, Children's Hospital of Alabama; Clinical Associate Professor, Division of Pediatric Neurology, University of Alabama at Birmingham
1996-2009 Our Lady of Peace Site Training Coordinator, Child Psychiatry Program, Assistant Clinical Professor, University of Louisville
1996-2009 Private Practice of Child and Adult Psychiatry, Louisville, Kentucky
2001-2002 Adolescent Unit Chief Psychiatrist, Riverview Hospital for Children and Youth, Middletown, CT
2002-2007 Clinical Director, Neurobehavioral Unit and Innovations Units, OLOP (Brain Injury, Autism and Mental Retardation Programs), Louisville
2009-Present Associate Professor of Child & Adolescent Psychiatry and Pediatrics, University of Florida College of Medicine, Gainesville, FL
2009-Present Division Chief, Child and Adolescent Psychiatry, Department of Psychiatry, University of Florida College of Medicine, Gainesville, FL

Other Experience and Professional Memberships

1989-1993 Consultant to community based Home Emergency Learning Project and Therapeutic Foster Care Programs, Seven Counties Services, Inc., Louisville, KY
1997-2001 Founding Clinical Directorships: Neurobehavioral Service and Innovations Developmental Service (MRDD) Caritas Peace Center, Louisville, KY

C. Selected peer-reviewed publications (in chronological order).

Heilman KM, Tucker DM, Valenstein E. A Case of Mixed Transcortical Aphasia with Intact Naming. *Brain* 1976 Sep;99(3):415-26.
Heilman KM, Gold MS, Tucker DM. Improvement of Aphasics' Comprehension by Use of Novel Stimuli. *Trans.*

Am Neurological Association 1975;100:201-2.
Tucker DM, Watson RT, Heilman KM. Discrimination and Evocation of Affectively Intoned Speech in Patients with Right Parietal Disease. *Neurology* 1977 Oct;27(10):947-50.
Peterson BP, Tucker DM. "Neuroimaging in Child Psychiatry," (chapter) in Melvin Lewis (ed.), *Textbook of Child and Adolescent Psychiatry*, Baltimore, Williams and Wilkins, 1996.
Tucker DM, Leckman JF, Scahill L, Wilf GE, LaCamera R, Cardona L, Cohen P, Heidmann S, Goldstein J, Judge J, Snyder E, Bult A, Peterson BS, King R, Lombroso P. A Putative Post streptococcal Case of OCD with Chronic Tic Disorder, Not Otherwise Specified. J Am Acad Child Adolesc Psychiatry. 1996 Dec;35(12):1684-91.
Dure LS, Tucker DM. Tourette Syndrome. *Current Opinion in Neurology* 1997 Apr;10(2):153-9.
Marques-Dias MJ, Mercadante MT, Tucker D, Lombroso P. Sydenham's chorea: a paradigm of neuropsychiatric autoimmune disorder. Psychiatr Clin North Am. 1997 Dec;20(4):809-20.
Peterson BS, Leckman JF, Tucker D, Scahill L, Staib L, Zhang H, King R, Cohen DJ, Gore JC, Lombroso P. Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention deficit/hyperactivity disorders. Arch Gen Psychiatry. 2000 Apr;57(4):364-72.
Luo F, Leckman JF, Katsovich L, Findley D, Grantz H, Tucker DM, Lombroso PJ, King RA, Bessen DE. Prospective Longitudinal Study of Children with Tic Disorders and/or Obsessive-Compulsive Disorder: Relationship of Symptom Exacerbations to Newly Acquired Streptococcal Infections. *Pediatrics:* 2004; 113; e578-e585.

D. Research Support.

None.

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Vollmer, Timothy R.	Full Professor
eRA COMMONS USER NAME	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Western Michigan University	N/A	N/A	Psychology
University of Florida	B.S.	1985	Psychology
University of Florida	Ph.D.	1992	Psychology

A. Personal Statement

The goal of the proposed research is to investigate behavioral rigidity among individuals with autism spectrum disorders. My aim is to contribute to this series of studies by virtue of my expertise in direct behavioral observation and measurement, single-subject experimental designs, applications involving shaping with percentile schedules of positive reinforcement, stimulus preference assessments, and intellectual disabilities/autism. I have published and presented extensively on these topics and have received considerable honors and appointments for my work in these realms. In addition, I am working currently with Dr. Lewis to establish a university wide autism research program ranging from basic research to front line application. The translational nature of the proposed study is in line with our over-arching professional and scientific goals.

B. Positions and Honors.

Professional Experience

1992-1996 **Assistant Professor (Psychology).** Louisiana State University, Baton Rouge Louisiana
1996-1998 **Associate Professor (Pediatrics)**, University of Pennsylvania School of Medicine
1998-2002 **Assistant Professor (Psychology),** University of Florida
2002-2007 **Associate Professor (Psychology),** University of Florida
2007-current **Professor (Psychology),** University of Florida

Academic Awards and Honors

1996. B. F. Skinner New Researcher Award. American Psychological Association, Div. 25
1996-2000 Associate Editor. Journal of Applied Behavior Analysis.
1998-2006 Appointed to Board of Directors, Society for the Experimental Analysis of Behavior
2004 Distinguished contributions to applied behavior analysis. Division 25, APA
2004-2006 University of Florida Research Foundation Professorship
2007-current Associate Editor. Behavior Analysis in Practice.
2008-current Associate Editor Mentor. Journal of Applied Behavior Analysis.
2008 Colonel Allan R. and Margaret G. Crow Term Professor. University of Florida College of Liberal Arts and Sciences.
2009 Elected to the executive council of the Association for Behavior Analysis International.
2010-current Re-appointed to Board of Directors, Socieity for the Experimental Analysis of Behavior.

C. Selected peer-reviewed publications (in chronological order, sample of 15 out of 113).

Vollmer, T.R., Roane, H.S., Ringdahl, J.E., & Marcus, B.A. (1999). Evaluating treatment challenges with differential reinforcement of alternative behavior. Journal of Applied Behavior Analysis, 32, 9-23.

Vollmer, T.R., Borrero, J.C., Lalli, J.S., & Daniel, D. (1999). Evaluating self-control and impulsivity in children with severe behavior disorders. Journal of Applied Behavior Analysis, 32, 451-466

Marcus, B.A., Swanson, V., & Vollmer, T.R. (2001). Effects of parent training on parent and child

behavior using procedures based on functional analyses. Behavioral Interventions, 16, 87-104.
Vollmer, T.R., & Hackenberg, T.D. (2001). Reinforcement contingencies and social reinforcement: Some reciprocal relations between basic and applied research. Journal of Applied Behavior Analysis, 34, 241-253.
Borrero, J.C. & Vollmer, T.R. (2002). An application of the matching law to severe problem behavior. Journal of Applied Behavior Analysis, 35, 13-26.
Bourret, J., Vollmer, T.R., & Rapp, J.T. (2004) Evaluation of a vocal mand assessment and vocal mand training procedures. Journal of Applied Behavior Analysis, 37, 129-144.
Rapp, J.T., Vollmer, T.R., St.Peter, C., St. Peter, C., & Cotnoir, N. (2004). Analysis of response allocation in individuals with multiple forms of stereotyped behavior.". Journal of Applied Behavior Analysis, 481-500.
Rapp, J.T. & Vollmer, T.R. (2005). Stereotypy I: A review of behavioral assessment and treatment. Research in Developmental Disabilities, 26, 527-547.
Sloman, K., Vollmer, T.R., Cotnoir, N., Borrero, C.S.W., Borrero, J.C., Samaha, A., & St.Peter, C.C. (2005). Descriptive analysis of parent reprimands. Journal of Applied Behavior Analysis, 38, 373-383.
Gutierrez, A. Vollmer, T.R., Dozier, C.L., Borrero, J.C., Rapp, J.T., Bourret, J., & Gadaire, D. (2007). Manipulating establishing operations to test for stimulus control during mand training. Journal of Applied Behavior Analsyis, 40, 645-658.
Dozier, C., Vollmer, T.R., Borrero, J.C., Rapp, J.T., Bourret, J., & Gutierrez, A. (2007). Assessment of preference for treatment versus baseline conditions. Behavioral Interventions, 22, 245-261.
Athens, E.A., Vollmer, T.R., & St. Peter Pipkin, C.C. (2007). Percentile schedules as a method of shaping academic task engagement. Journal of Applied Behavior Analysis, 40, 475-488.
Athens, E.S., Vollmer, T.R., Sloman, K.N., & St. Peter Pipkin C.C., (2008). An analysis of vocal stereotypy and treatment schedule thinning. Journal of Applied Behavior Analysis, 41, 291-297.
St. Peter Pipkin, C., & Vollmer, T.R. (2009). Applied implications of reinforcement history effects. Jounal of Applied Behavior Analysis, 42, 83-103.
Samaha, A.L., Vollmer, T.R., Borrero, C., Sloman, K., Pipkin, C., & Bourret, J. (2009). Analyses of response-stimulus sequences in descriptive observations. Journal of Applied Behavior Analysis, 42, 447-468.

D. Research Funding in last three years

2007 (PI)—Seguin Behavioral Services. Tacachale/Agency for Persons with Developmental Disabilities. 2007-2008.
2007 (PI)—University of Florida Behavior Analysis Services Program. Florida Department of Children and Families.
2008 (PI)—Heartland for Children University of Florida Behavior Analysis. Heartland for Children Agency.
2008 (PI)—University of Florida Behavior Analysis Services Program, Florida Department of Children and Families.
2008 (PI)— Seguin Behavioral Services. Tacachale/Agency for Persons with Developmental Disabilities.
2009 (PI)—Heartland for Children University of Florida Behavior Analysis. Heartland for Children Agency.
2009 (PI)-- Seguin Behavioral Services. Tacachale/Agency for Persons with Developmental Disabilities.
2010 (PI)—Addendum--Heartland for Children University of Florida Behavior Analysis. Heartland for Children Agency.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

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

Prefix:	Dr.
* First Name:	Mark
Middle Name:	H.
* Last Name:	Lewis
Suffix:	PhD

2. Human Subjects

Clinical Trial? ☒ No ☐ Yes

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

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix:	Dr.
* First Name:	Thomas
Middle Name:	E.
* Last Name:	Walsh
Suffix:	PhD
* Phone Number:	352-392-1582
Fax Number:	352-392-4400
Email:	ufawards@ufl.edu
* Title:	Director of Research
* Street1:	219 Grinter Hall
Street2:	Box 115500
* City:	Gainesville
County/Parish:	Alachua
* State:	FL: Florida
Province:	
* Country:	USA: UNITED STATES
* Zip / Postal Code:	32611-5500

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells

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

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

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

Tracking Number:GRANT10655481 Funding Opportunity Number:PA-10-069 Received Date:2010-07-16T09:31:46-04:00

PHS 398 Modular Budget, Periods 1 and 2

OMB Number: 0925-0001

Budget Period: 1

Start Date: 04/01/2011 End Date: 03/31/2012

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	150,000.00
Consortium F&A	
* Total Direct Costs	150,000.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	MTDC	46.5	140,530.00	65,346.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS
Darryl Mayes
202-401-0215

Indirect Cost Rate Agreement Date: 06/02/2009

Total Indirect Costs: 65,346.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($): 215,346.00

Budget Period: 2

Start Date: 04/01/2012 End Date: 03/31/2013

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	125,000.00
Consortium F&A	
* Total Direct Costs	125,000.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	MTDC	46.5	114,110.00	53,061.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS
Darryl Mayes
202-401-0215

Indirect Cost Rate Agreement Date: 06/02/2009

Total Indirect Costs: 53,061.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($): 178,061.00

Tracking Number:GRANT10655481 Funding Opportunity Number:PA-10-069 Received Date:2010-07-16T09:31:46-04:00

PHS 398 Modular Budget, Periods 3 and 4

Budget Period: 3

Start Date: End Date:

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

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

Indirect Cost Rate Agreement Date

Total Indirect Costs

C. Total Direct and Indirect Costs (A + B) Funds Requested ($)

Budget Period: 4

Start Date: End Date:

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

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

Indirect Cost Rate Agreement Date

Total Indirect Costs

C. Total Direct and Indirect Costs (A + B) Funds Requested ($)

PHS 398 Modular Budget, Periods 5 and Cumulative

Budget Period: 5

Start Date: | End Date:

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

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

Indirect Cost Rate Agreement Date

Total Indirect Costs

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($)

Cumulative Budget Information

1. Total Costs, Entire Project Period

*Section A, Total Direct Cost less Consortium F&A for Entire Project Period	$	275,000.00
Section A, Total Consortium F&A for Entire Project Period	$	
*Section A, Total Direct Costs for Entire Project Period	$	275,000.00
*Section B, Total Indirect Costs for Entire Project Period	$	118,407.00
*Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period	$	393,407.00

2. Budget Justifications

Personnel Justification	1243-Personnel_Justification.p	Add Attachment	Delete Attachment	View Attachment
Consortium Justification		Add Attachment	Delete Attachment	View Attachment
Additional Narrative Justification		Add Attachment	Delete Attachment	View Attachment

Tracking Number:GRANT10655481 Funding Opportunity Number:PA-10-069 Received Date:2010-07-16T09:31:46-04:00

Personnel Justification

Mark H. Lewis, Ph.D., Principal Investigator (2.40 calendar months), will have overall responsibility for the conduct of the proposed studies and will be involved in all phases of the project.

Timothy R. Vollmer, Ph.D., Investigator (2.40 calendar months), will work directly with the P.I. in establishing the conditions for the observational study, developing the intervention, training therapists and evaluating treatment efficacy and fidelity.

Krestin J. Radonovich, Ph.D., Investigator (0.84 calendar months in Year 1 and 0.60 in Year 2), is a child neuropsychologist with experience in the assessment and treatment of children with autism. She will work directly with the P.I. on all aspects of subject assessment and evaluation.

Soo-Jeong Kim, M.D., Investigator (0.60 calendar months in Year 1 and 0.30 in Year 2) is a child psychiatrist with specific expertise in autism. She will be involved in diagnostic assessments and recruitment efforts.

Daniel K. Tucker, M.D., Investigator (0.30 calendar months in Year 1 only) is a child psychiatrist with extensive experience in autism. He will be involved in diagnostic assessment, recruitment efforts.

TBN Graduate Student Assistants (2 at 6.0 calendar months each), who will work directly with Dr. Vollmer to conduct the observational an intervention studies. They will also be involved in training undergraduate therapists and parents.

OMB Number: 0925-0001

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

☐ New ☒ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application (for RESUBMISSION or REVISION only)	1244-Introduction.pdf	Add Attachment	Delete Attachment	View Attachment
2. Specific Aims	1245-Specific_Aims.pdf	Add Attachment	Delete Attachment	View Attachment
3. *Research Strategy	1246-Research_Strategy.pdf	Add Attachment	Delete Attachment	View Attachment
4. Inclusion Enrollment Report		Add Attachment	Delete Attachment	View Attachment
5. Progress Report Publication List		Add Attachment	Delete Attachment	View Attachment

Human Subjects Sections

6. Protection of Human Subjects	1247-Human_Subjects.pdf	Add Attachment	Delete Attachment	View Attachment
7. Inclusion of Women and Minorities	1248-Women-Minorities.pdf	Add Attachment	Delete Attachment	View Attachment
8. Targeted/Planned Enrollment Table	1249-Targeted-Planned_Enrol	Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Children	1250-Children.pdf	Add Attachment	Delete Attachment	View Attachment

Other Research Plan Sections

10. Vertebrate Animals		Add Attachment	Delete Attachment	View Attachment
11. Select Agent Research		Add Attachment	Delete Attachment	View Attachment
12. Multiple PD/PI Leadership Plan		Add Attachment	Delete Attachment	View Attachment
13. Consortium/Contractual Arrangements		Add Attachment	Delete Attachment	View Attachment
14. Letters of Support		Add Attachment	Delete Attachment	View Attachment
15. Resource Sharing Plan(s)	1251-Resource_Sharing.pdf	Add Attachment	Delete Attachment	View Attachment

16. Appendix Add Attachments | Remove Attachments | View Attachments

INTRODUCTION

CRITIQUE 1:

Premise of a negative effect of higher order restricted and repetitive behaviors on the development of functional behaviors and developmentally complex repertoires is not well documented. **We agree and have amended the application (see Specific Aims).**

Although the focus of the application is on higher order RRB in higher functioning children… **We are focused on restricted, inflexible behavior in the context of age appropriate everyday activities and not focused on specific RRBs in either higher or lower functioning individuals.**

Justification for studying typically developing children age 6-12 years is not supported by the literature cited. **Justification is now provided in the amended application**

Assumption that higher order RRB has a distinct cognitive component … appears at odds with an operant intervention approach. **Our intervention approach is focused on the restricted, inflexible features of observable behavior independent of cognitive mediation.**

The application lacks elaboration of the role of the behavior rating scales ... **We have eliminated the scales.**

…there is a strong possibility that the structured settings will not elicit the target behaviors. **We are not trying to elicit target behaviors but rather focused on restricted inflexible responding in the context of interacting with standardized activities (see also Potential Pitfalls section).**

Further justification is needed regarding the inclusion of TD children – particularly in the age range under study. **This justification is now included in the amended application.**

RRBs constitute a broad category and … some forms are more amenable to the proposed intervention than others. **We are not targeting specific RRBs but rather inflexible responding to specific standardized activities.**

The data analysis strategy for Specific Aim 1 … (and) Specific Aim 2. **Addressed in the amended application.**

The study includes an unpublished scale of interests… **We have eliminated this scale from the proposed study**

The standardized setting is not well described. … what procedures will be in place to preserve the integrity of that setting from one session to the next? **A standard set of activities/materials with a schematic of every item in the testing room and its location provided to the research team to insure session to session standardization.**

CRITIQUE 2

No operational definition(s) of inflexible behavior are provided. **Provided in the amended application.**

… one would almost by necessity have to conduct some preliminary observations … **We propose to examine restricted, inflexible behavior in the context of specific, standardized activities and we have now operationalized restricted, inflexible responding in the context of those activities.**

… potential patterns of responding that do not readily lend themselves to a single, multiple-baseline design. **We now propose several nonconcurrent multiple baseline designs both within and across subjects.**

…contingent access to a highly preferred, restricted and repetitive response? **Will be used if the preference assessment indicates.**

…not clear how the investigators will determine whether the intervention produces a generalized reduction in inflexible response patterns beyond the specific response targeted during treatment." **Generalization is beyond the scope of this project but will be addressed in future studies following demonstration of efficacy.**

CRITIQUE 3

Aim 2 seems to have much greater potential to significantly impact scientific knowledge and clinical practice than does completion of Aim 1. It is unlikely that an observational assessment as lengthy as that proposed … would be feasible or practical ... **Aim 1 will provide new and important information to the field and a critical standard against which to assess and provide treatment to ASD children. We have reduced the observational assessment to two 30 min sessions.**

The observational assessment proposed is novel, but unlikely to shift current research or clinical practice paradigms … **Aim #1 is needed to establish the empirical foundation for our intervention approach and, hopefully, for changes in clinical research and practice. If we (and others) provide strong evidence for differences in ASD and TD children in how restricted or inflexible they are in engaging in daily activities, then there will be a solid rationale for a shift in clinical treatment studies and practice.**

Given the inconclusive empirical evidence with regard to cognitive inflexibility and RRB... **We have eliminated assessment of cognitive flexibility from the proposed studies.**

Requiring the SCQ score of 18 or greater may be a concern for participant ascertainment. **We have now lowered the SCQ cut-off score.**

It is not clear how the assessment or intervention assess or treat circumscribed/unusual interests, if they do. What if fewer than 10 of the 20 demonstrate excessive problems with restricted, repetitive behaviors? **Both assessment and intervention target restricted, inflexible behavior in the context of engaging with specific, standardized activities. Given that we have proposed a single-subject design, we do not need to achieve a particular N for statistical power purposes but believe that n=10 will provide compelling evidence for replication of treatment effects.**

SPECIFIC AIMS

Autism spectrum disorders (ASD) are defined, in part, by behavior that can be characterized as restricted and inflexible. Such behavior is exemplified by the so-called “higher order” restricted repetitive behaviors characterized by their insistence on sameness or resistance to change. Behaviors characterized in this way are pervasive in children with ASD and constitute a significant challenge for parents and caregivers. To the extent to which restricted behaviors and interests and rigidity or inflexibility characterize a child’s repertoire, opportunities to develop functional behaviors and more complex behaviors would seem limited. The overall goal of the proposed project, then, is to initiate a program of research to develop a novel treatment approach to restricted, inflexible behavior, a clinically important and highly understudied problem in ASD. Rather than target a particular compulsive, restricted, or repetitive behavior for modification, our proposed strategy is to promote the development of flexibility and variability. This will be done using activities with which children in our targeted age range will likely engage, based on our previous experience. As such, the proposed project is highly translational as our approach to intervention is based on a set of animal and human laboratory studies that have established the empirical foundation for such an approach. Effective interventions are hypothesized to have generalizable effects on development and will be highly translatable to other neurodevelopmental disorders for which restricted, inflexible behavior is problematic. Thus, we propose to assess restricted, inflexible behavior in children with ASD and typically developing controls and then pilot test a behavioral intervention to determine if it will directly promote variable and flexible adaptive responding in children with ASD. No systematic efforts have been made to develop effective methods for the behavioral treatment of the general rigidity/inflexibility that is most characteristic of autism and common in related neurodevelopmental disorders. Thus, this project is highly innovative in targeting flexibility and variability as goals of the intervention. Finally, the proposed project represents a translational effort to take laboratory-based studies and apply them to a focused intervention directed at restricted, inflexible behavior that can ultimately be conducted in a community setting. If successful, the proposed treatment approach should have considerable potential for becoming a widely used, cost effective treatment approach. To achieve this goal, we will pursue the following specific aims:

Specific Aim #1: Assess restricted inflexible behavior in ASD and typically developing children using direct observations of behavior

We will collect observational data of restricted, inflexible behavior in a standardized environment. Direct observations of both typically developing (TD) and ASD children will be coded to provide multiple objective measures of restricted, inflexible behavior. This observational study will be the first of its kind to assess restricted, inflexible behavior in the context of age-appropriate, everyday activities. Thus, we anticipate that successful completion of this aim will provide the first set of direct observations focused on restricted, inflexible behavior and the first systematic comparison of observable inflexible behavior in ASD versus TD children. As restricted, inflexible behavior is part of normative development, this study will be of considerable importance in characterizing the restricted, inflexible behavior of children with ASD in comparison to typically developing children of the same age and level of functioning. We will assess the number, duration, and sequence of activities engaged in as well as the number, duration, and sequences of response choices employed within an activity. Importantly, these measures will serve as targets for intervention for the ASD children participating in the proposed treatment study. Moreover, the data collected using TD children will provide an important standard against which to assess treatment gains in ASD children in Aim #2.

Specific Aim #2: Pilot test an intervention for promoting variable and flexible responding in ASD children

Basic animal and human operant studies have demonstrated experimental control of variable/flexible responding. Indeed, there have been demonstrations that some forms of increased variability can be attained in children with autism using reinforcement procedures. Thus, we hypothesize that individuals with autism can learn more flexible, variable patterns of responding. Using the same standardized environment and activities as in Aim #1, we will pilot an intervention strategy that extends basic laboratory studies and provides proof of concept of our proposed intervention approach. This intervention strategy will make use of single subject methodology including percentile schedules of reinforcement. Extending work completed in Aim #1, we will shape increased variability or flexibility in the number and sequence of activities engaged in, as well as in the number and sequence of potential responses within an activity.

RESEARCH STRATEGY

SIGNIFICANCE AND INNOVATION

Restricted, Inflexible Behavior and Autism

Children with ASD often follow fixed routines (e.g., wearing the same clothes, eating the same meal everyday), show intense attachments to objects or unusual preoccupation with objects (e.g., vacuum cleaners), and exhibit limited play patterns. In addition, they exhibit intense, circumscribed interests (e.g., train schedules), perseverate in their use of language, and are rigid and intolerant of new situations and changes in their environment. Moreover, given the sometimes catastrophic reaction to change observed in children with autism, parents frequently go to great lengths to accommodate to the rituals or need for sameness exhibited by these children. This restricted and inflexible behavior can preclude children with autism from responding adaptively and flexibly to their environment. Despite the clinical significance of restricted, inflexible behavior, the literature devoted to the study of this domain in autism is quite small in comparison with the extensive literature on social and communication deficits (Lewis & Bodfish, 1998; Cuccaro et al., 2003; Lopez et al., 2005).

Inflexible behavior in individuals with ASD has been apparent in experimental tasks as well. For example, Baron-Cohen (1992) using a hide-a-penny task, showed that children with autism were more likely to generate a simple, predictable pattern, such as repeatedly switching back and forth from left to right hands. Mullins and Rincover (1985) asked children with and without autism to pick one of five cards, behind which food was placed on different schedules of reinforcement. Control participants sampled all five alternatives and quickly learned to choose the most frequently reinforced card. Children with autism sampled only a limited number of cards and thus often preferred a non-optimal alternative. Frith (1972) reported that TD and developmentally disabled children showed greater sequence complexity and more colors, when asked to place colored stamps on paper, than children with autism. When asked to choose one of two arms of a T-maze, ASD children repeatedly chose one arm, whereas the controls varied between the two (Boucher, 1977). Finally, individuals with ASD exhibit greater sequence regularity than controls in random number generating tasks (Williams et al., 2002; Rinehart et al., 2006).

Promoting flexibility and variability: basic laboratory studies

There is a small but compelling literature that has demonstrated empirically that it is possible to shape variable, flexible behavior using reinforcement procedures. Neuringer (2004) has reviewed these basic animal and human laboratory studies which show that variability can be learned and maintained through reinforcement. Of particular relevance to the present application, are the few demonstrations in individuals with autism of increased variability in responding achieved through reinforcement procedures. For example, Goetz and Baer (1973) demonstrated that preschoolers could be taught to engage in more variable and flexible play behavior using social reinforcement procedures. By reinforcing only the first observed within-session occurrence of forms constructed with blocks, they were able to increase the number of novel constructions. Miller and Neuringer (2000) showed that participants with autism varied significantly less than controls, but when reinforced, variability increased significantly in both groups. This strategy was extended to the language and communication domain by Lee et al. (2002). These investigators shaped varying appropriate verbal responses to a single social question to which three individuals with autism always gave the same answer. These studies involved a small number of individuals and provide “proof of principle” for the notion that at least some forms of variability or flexibility in responding can be considered an operant and shaped through reinforcement procedures. We wish to build on this approach and extend it to an effective intervention program in children with autism.

Restricted, inflexible behavior: Assessment and intervention

Few attempts have been made to directly measure and quantify restricted, inflexible behavior, and this lack of assessment hampers treatment efforts. As far as we know, there have been no systematic attempts to develop an intervention model to address restricted, inflexible behaviors in ASD. Thus, the focus of this application is a clinically important and highly understudied problem in neurodevelopmental disorders in general and autism in specific. The proposed project will adopt a treatment strategy based on a small but compelling set of results from basic behavioral studies conducted in animals and humans that targeted increased variability and flexibility in behavior as its goal. This novel approach to treatment reflects a translational research approach to autism such that the laboratory-based investigations can progress to focused interventions designed to target the core problem of inflexible behavior and conducted in children’s typical environments. Rather than target a particular compulsive, restricted, or repetitive behavior for

modification, our proposed strategy is to promote the development of flexibility and variability in functional activities. The impact of such an intervention promises to have widespread effects and, indeed, when extended to young children may significantly attenuate the development of restricted, inflexible behaviors. If shown to be feasible and effective, this treatment can be easily exported to a parent or teacher driven intervention and generalized to home, school, or daycare environments. It can also be adapted for younger children with ASD. In addition, increases in variability and flexibility can be sought in multiple domains including social and language/communication behavior. Finally, such a therapeutic approach would have great generalizability to other neurodevelopmental disorders which exhibit considerable restricted, inflexible behavior. Establishing ways to assess variability and flexibility in daily activities and developing ways to increase variability and flexibility in responding will be of significant benefit to individuals with autism and their families. Moreover, the proposed treatment approach should have considerable potential for becoming a widely used, cost effective treatment approach.

APPROACH

A NIMH working group recently provided guidelines for designing research studies of psychosocial interventions for individuals with ASD (Smith et al., 2007). This working group identified “formulation and systematic application of a new intervention technique” as Phase 1 and the current application proposes work relevant to this first phase.

Research Participants

We will recruit children diagnosed with ASD who (1) have received clinical diagnoses based on the DSM-IV diagnostic criteria, (2) have a score equal to or above 15 on the Social Communication Questionnaire (SCQ) (Berument et al., 1999), (3) meet criteria for ASD by the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 1999), and (4) have a nonverbal IQ equal to or greater than 80. ASD children that 1) have been maintained on a stable (3 months) regimen of psychoactive medication, 2) have co-morbid psychiatric diagnoses (e.g., ADHD), and 3) have a history of or current dietary, allied health (e.g., speech, OT) intervention will *not* be excluded. However, ASD children currently enrolled in a formal behavioral intervention program (30 hours or greater per week, overseen by a licensed practitioner; e.g., ABA or EIBI) will be excluded.

For Aim 1, TD children, matched to the ASD children on gender, age and level of intellectual functioning, will be asked to participate. TD children will *not* have a diagnosis of ASD, intellectual and developmental disability, or any other psychiatric or neurological diagnosis. We will use the NIMH Diagnostic Interview Schedule for Children Version (DISC-2.3) (Shaffer et al., 1996) to verify the TD children do not have any psychiatric diagnosis. In addition, we will also administer the SCQ to verify the TD children do not have an autism phenotype. For this purpose, we will use a cut off score of 10 (Charman et al., 2007; Bishop et al., 2006). We will recruit typically developing children to reflect the gender ratio expected in the ASD group.

We will exclude children (either ASD or TD) who (1) have neurological disorders (i.e., seizures, tumor, severe head injury, stroke, brain lesion or disease), (2) are not ambulatory, and (3) have significant visual or auditory sensory impairment.

Using TD controls for Aim 1 will be important as restricted, inflexible behavior is normative during certain developmental periods. For example, in the preschool years, TD children begin to exhibit complex repetitive behaviors that are characterized by a surprising rigidity or inflexibility (Evans et al., 1997; DeLoache et al., 2007). In addition, levels of restricted, inflexible behavior in TD children will provide a standard against which to assess treatment gains in Aim #2. Thus, we believe there is a compelling rationale for including TD children in these studies.

We chose 6-12 years as our participant age range, as restricted, inflexible behaviors in ASD children will be increasing or asymptotic during this period (Richler et al., 2010) whereas these behaviors will have declined in TD children by this age (Evans et al., 1997). Moreover, Kimberg (2009) found no difference between ASD and TD pre-schoolers (4-5 years of age) in either the number of different block forms created or the sequence of repeated block forms. Thus, use of this age range should result in significant group differences in Aim #1. Finally, using somewhat older, higher functioning children will increase the feasibility of developing and testing our proposed intervention. We do appreciate, however, that ultimately our intervention needs to be modified for use with young children and lower functioning children as part of an overall effort aimed at early intensive intervention.

Recruitment

Significant resources are available for recruiting participants including the University of Florida Center

for Autism and Related Disabilities (UF-CARD) which is administratively housed in the Department of Psychiatry and McKnight Brain Institute, and serves a geographical region of 14 counties and has a current constituency of about 1600 individuals. The P.I., Dr. Lewis serves as Executive Director of CARD and Dr. Radonovich, a Co-Investigator on this project, devotes 40% effort to CARD activities. Additionally, the UF Division of Child and Adolescent Psychiatry provides outpatient services to children with autism and their families. Assessments and evaluations are provided to approximately 12 new children and their families per month. Drs. Tucker and Kim, co-investigators on this application, provide such care. Typically developing children will be recruited by advertising in the community. We will also recruit siblings of ASD participants if they provide appropriate matches for specific children in the ASD group. Finally, Dr. Vollmer's program routinely receives requests for participation in behavioral research relating to autism.

Diagnostic Assessments

Diagnostic assessments for ASD participants will include the Autism Diagnostic Observation Schedules (ADOS) (Lord et al., 1999). Both ASD and TD children will be administered the Social Communication Questionnaire (SCQ) (Berument et al., 1999). Cognitive function will be measured by the Leiter International Performance Scale-Revised (Leiter-R) (Tsatsanis et al., 2003) in both the ASD and TD subjects. Adaptive function will be assessed by the Vineland Adaptive Behavior Scale, 2nd edition (VABS-II, (Sparrow & Cicchetti, 1985; Carter et al., 1998) in both ASD and TD children. For TD children only, the NIMH Diagnostic Interview Schedule for Children Version (DISC-2.3) (Shaffer et al., 1996) will be administered to exclude children with specific forms of psychopathology in the TD group.

Specific Aim #1: Assess restricted inflexible behavior in ASD and typically developing children using direct observations of behavior

Experimental Setting and Materials

We will construct a standardized setting that will involve a comfortable room with unobtrusive video recording equipment and a set of six activities that, based on our previous experience, should generally appeal to children of the proposed age group. The six different activities will include: a set of video clips, rubber stamps with ink pads, puzzles, coloring implements (crayons, markers), building blocks, and stickers. The materials to be used for each of these activities will differ across three age ranges 6-8, 8-10, and 10-12 years in order to insure age appropriateness and thus likelihood of engagement. So, for example, for building blocks, we would use foam blocks for the youngest children, wooden building blocks for 8-10 year olds, and LEGO® blocks for the 10-12 year olds. Moreover, each activity will have a specified set of response choices which can be done in a variety of sequences. For example, participants will have six short video clips available allowing us to determine the number of response choices (clips) selected and the sequence (e.g., the child opts to view only 2 of the clips but 4 times each, exhibiting the following clip number sequence: #3, #6, #3, #6, #3, #6, #3, #6). Importantly, engagement in each activity will not depend on a fixed temporal order of the response choices.

The setting including specific location of objects will be the same across all sessions. A schematic of every item in the testing room and its location will be provided to the research team to insure session to session standardization. We will assess children individually and an investigator will be in the room with the child. The investigator will provide a general instruction at the beginning to the effect that the child is free to go play with any of the activities available.

Observational Methods

We will video record each subject in this experimental setting for 30 minutes on two different occasions, separated by approximately one week, in order to assess restricted, inflexible behavior. During the first session, the child will be free to interact with the activities without any prompts from the observer. On the second session, the observer will provide the participant with a single verbal prompt to switch activities. This prompt will be given 5 times (every 5 minutes) during the 30 minute session. This manipulation will aid in determining group differences in flexible responding and allow for observation of variability in responses and response sequence.

The observation sessions will be timed to coincide with periods of the day (e.g. after school) that are largely leisure/recreational time for the child and times that result in minimal inconvenience for the family. Video recordings will be coded using The Observer system (Noldus, Netherlands). We have considerable experience with observational methods and will use raters who have established inter-rater reliability (Cohen's kappa >0.70). In addition, we will periodically assess inter-rater reliability to prevent observer drift. Advanced

undergraduate students that have relevant coursework and experience with observational methods will serve as coders.

We will operationalize restricted, inflexible behavior by assessing: 1) the activities in which the child engages including number of activities, duration of engagement with each activity, and the sequence of engagement with the activities; and 2) for any single activity, the number, duration, and sequence of potential response choices. For example, an individual child may engage in 4 of the 6 activities, engaging in each activity only once during the session for 4, 7, 3, and 9 minutes each. One of those activities is drawing with markers and the child uses 2 of 8 different color markers for 2 (blue), 1 (green), 3 (blue) and 2 (green) minutes. Thus, we will code 1) the number 2) the duration and 3) the sequence of activities or response choices within an activity.

Experimental Design

We will adopt a two group design and compare children with ASD and TD matched control children on the proposed multiple measures of restricted, inflexible behavior. We hypothesize that children with autism will exhibit a reduced number and sequence of activities, and, within an activity, a reduced number and sequence of potential response choices. Given the large effect size expected, we anticipate needing a relatively small number of research participants to find a statistically significant difference between groups. As there are no relevant findings in the literature on which to base an estimated effect size, we will continuously update power calculations based on preliminary data. At this point, however, we anticipate enrolling 20 children per group (N=40). Standard multivariate techniques will be used to test group differences across our specified dependent measures.

Anticipated Outcomes and Potential Pitfalls

We anticipate that successful completion of Aim #1 will provide the first set of direct observations focused on restricted, inflexible behavior, made during age appropriate activities in a controlled setting and directly compared to matched typically developing controls. Perhaps the most serious potential pitfall would be that the setting and activities selected may not provide the necessary context to observe robust differences in restricted, inflexible responding between TD and ASD children. If so, we will test the effect of replacement with other activities including, for each participant whether TD or ASD, at least one highly preferred activity based on parent report. The proposed study is among the first to construct a coding system to capture variable/flexible responding. We do, however, have considerable expertise and experience in developing and applying coding systems to capture both animal and human behavior.

Specific Aim #2: Pilot test an intervention for promoting variable and flexible responding in ASD children

Rationale

The NIMH working group on psychosocial interventions for individuals with ASD (Smith et al., 2007) suggested that the goal of the first phase of research should be an initial efficacy study to refine intervention techniques and conducting initial efficacy studies as ‘proof of concept” using case studies or, if possible, to test the method with an experimental research design. In the view of this working group, single-subject experimental designs are particularly appropriate for this phase as these designs allow for a determination of clear, replicable effects, multiple opportunities to refine and individualize intervention techniques, and can be conducted efficiently by small research teams. Thus, we propose to conduct a pilot study using a single subject experimental design to determine the feasibility and acceptability of our approach.

Research Participants

We anticipate enrolling 10 children with ASD who have participated in the observational study described under Aim 1. As we are proposing single subject methodology, this number is somewhat arbitrary but should provide more than adequate replication across subjects (Cooper et al., 2007). Inclusion/exclusion criteria and diagnostic assessments will be as previously described. These 10 participants will be children who clearly exhibited restricted, inflexible behavior in the observational study.

Experimental Design

The intervention will be conducted in the same experimental setting used for the observational study and make use of the same set of six activities. We will use a multiple baseline across participants design to demonstrate the specificity of the intervention in promoting flexible, variable responding. We will also utilize a

multiple baseline across activities design for each participant. For example, if an individual subject shows restricted, inflexible responding with respect to number of response choices within all activities, we will target responding in each activity sequentially. We will also occasionally employ a reversal design to further demonstrate experimental control by the reinforcement contingencies in effect.

During the baseline condition, sessions will last a total of 30 minutes, during which we will code restricted, inflexible behavior in the same manner described for Aim #1: number, duration, and sequence of both activities and response choices within an activity. We will employ two baseline components, each lasting 15 minutes, within each session with the order of the two baseline conditions being counterbalanced across sessions. The first baseline component will not involve any prompts whereas the second baseline component will involve verbal prompts presented five times during the 15 minutes. This will permit us to assess to what degree participants will change activities spontaneously and in response to a single verbal prompt. As we are proposing a multiple baseline across participants, the number of baseline sessions will, of course, vary among participants. For any one participant, however, we will rely on visual inspection to establish stability of responding before initiating the intervention phase of the study. We will initiate intervention when the target measure is stable, and a sufficient number of sessions have been conducted to ensure a stagger in the baselines appropriate for a multiple baseline across subjects design. The measure chosen for determination of stability will depend on the responding of the participant in baseline (e.g., number of activities, sequence of response choices).

Using baseline data, we will establish individual targets for intervention. For example, if an individual participant fails to engage in any activity then the first target for intervention will be to shape engagement in at least one activity for at least 5 minutes. If an individual participant is following a fixed sequence of activities, we will target increased sequence variability. If an individual focuses on one and only one activity throughout the session, we will shape engagement with at least one other activity for at least 5 minutes. With regard to a single activity, if an individual participant is using the same response choice (e.g., using only the blue marker) each time then a target will be to increase the number of response choices (markers of other colors). Similarly, if the participant follows a rigid sequence (red, blue, red, blue, etc.) in interacting with the activity then the target will be to shape more variable sequences.

Performance criteria or criteria to judge the success of the intervention will include four consecutive sessions where the target response is clearly outside the baseline range (e.g., an average of 4 activities engaged in vs. 2 at baseline) and where responding is stable (i.e., no upward or downward trend across sessions). An additional important aid in determining success of the intervention will be the results of the observational study conducted with TD children. The level of variability/flexibility exhibited by the TD control children will be used as an important standard against which to evaluate treatment gains. For example, we will compute differences in various measures between the ASD participant and the TD group and establish reducing that difference by half as one criterion for success.

We will work with each participant daily during weekdays for 30 minutes per day. During these sessions, the therapist will provide the participant with prompts to switch activities or, for any single activity, to switch response choices. These prompts will be given 5 times (every 5 minutes) during the session. We will adopt a three step prompting sequence moving successively from verbal to gestural/model to physical guidance if needed. For parts of selected sessions, the therapist will withhold prompts to determine the occurrence of unprompted switching.

We will use graduate students in the Experimental Analysis of Behavior program of the Department of Psychology as therapists. These students will be Masters prepared, will be under the direct supervision of Dr. Vollmer, and will have already achieved the designation of Board Certified Behavior Analyst which is a national certification.

Finally, a very important goal of this phase of the project is the assessment of treatment acceptability to parents. Thus, we will work closely with parents to insure that the procedures we are employing are acceptable to them. Generalization of treatment gains is, of course, a critical consideration. This is outside the scope of the R21, however, but can be assessed in future studies if we are able to establish treatment efficacy.

Methodology for Shaping Variability/Flexibility

The method we propose to shape more variable and flexible behavior will make use of percentile schedules of reinforcement (Galbicka, 1994). Such a schedule involves continuous updating of the reinforcement criterion based on the most recent responses of the individual. These responses are ranked (least to most) and the criterion for reinforcement is set such that a response must fall at or below/above a pre-established rank (e.g., the median rank). Thus, reinforcement contingencies are changing concomitantly with

current levels of responding and a standard criterion for reinforcement can be used with all research participants regardless of individual levels of absolute responding. Machado (1989) used a percentile reinforcement schedule to generate variability in the pattern of key pecking emitted by pigeons. Miller and Neuringer (2000) also used a percentile schedule to reinforce children with autism for varying their sequence of responses while playing a computer game.

We recently published the only study to date using percentile schedules to shape academic task engagement with special education students (Athens et al., 2007). The results showed that students' duration of engagement on academic tasks was increased by at least twofold and in some cases as much as fivefold over baseline duration means. We also found that when percentile schedule conditions involved a sampling of a greater number of prior observations in order to construct the percentile and response value, the percentile schedules were more effective than when fewer prior observations were used. This study provides evidence that percentile schedules can be used to increase durations of time spent on relatively less preferred activity. The method can be easily transported to the proposed intervention insofar as our aim is to increase durations of time spent on novel or at least relatively less preferred activities.

The percentile schedule of reinforcement should allow us to reinforce variability/flexibility even in the case of a child with severe restricted, inflexible behavior. In this situation, we will employ a sequence of prompts (verbal, gestural, physical) to obtain a switch to another activity. We do appreciate that prompting may induce problems behaviors reflective of a resistance to change so we will be very cognizant of that possibility during this stage of the intervention. We should note here that Dr. Vollmer and his students have considerable expertise and experience in the use of effective prompting and in the management of problem behaviors should they be exhibited.

Reinforcer Preference Assessment

A critical piece of the proposed intervention is our ability to identify stimuli that can be effectively used to reinforce more varied or flexible responding. The identification of reinforcing stimuli for individuals with ASD can prove to be challenging in many cases. Fortunately, assessment methodologies for identifying reinforcers have been developed and include techniques such as personal nomination, reinforcer surveys, and single-, paired- or multiple-stimulus presentations (Roane et al., 1998). Dr. Vollmer, a co-investigator on this project, has developed a brief stimulus preference assessment that involves free access to an array of stimuli (Roane et al., 1998). This assessment was shown to identify preferred stimuli that were differentially effective as reinforcers compared to non-preferred stimuli. In addition, it was shown to require less time to complete than a standard paired-stimulus preference assessment. Because of its brevity it can be repeated frequently throughout an intervention program. We will use this brief preference assessment method to identify reinforcing stimuli that can be used in the proposed intervention. In addition, we will employ other methods in identifying potential reinforcers including parent interviews. It is likely that food or other treats may be effective and that the child's preferred activity (including a restricted, inflexible behavior) could be used as a reinforcer, although in this case, we will need to determine how to restrict access to this activity.

Anticipated Outcomes and Potential Pitfalls

We anticipate that successful completion of this aim will provide proof of concept of our proposed treatment approach. We appreciate that operationalizing variability/flexibility for shaping by reinforcement procedures will be a challenge but the findings of the direct observation study (Aim #1) will guide this effort.

FUTURE DIRECTIONS

The NIMH working group on psychosocial interventions in autism (Smith et al., 2007) indicated that the second phase of designing a novel intervention should involve development of a treatment manual and a research plan for evaluation of the intervention. According to this working group, the goals for this phase should be assembling efficacious interventions into a manual, establish measures of treatment fidelity, test the feasibility of implementing the manuals across sites, evaluate the acceptability of the intervention to clinicians and families, and examine the feasibility of conducting the intervention in a community setting. Thus, in future studies, we propose to formalize a treatment protocol, assemble a manual, train therapists, conduct a formal test of the intervention in a controlled setting, pilot test and then formally test the intervention in the home setting, and train parents to function as therapists. During these phases we will assess treatment fidelity and acceptability of the intervention to parents.

Protection of Human Subjects

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics: We will recruit children diagnosed with autism spectrum disorders between the ages of 6 and 12 years who are higher functioning. Our target sample size for this project will be 20 children with ASD and 20 TD control children. For the studies subsumed under Aim 1, typically developing children also will be asked to participate. These children will be matched to the ASD children on gender, age and level of intellectual functioning.

Inclusion criteria for the ASD group: Children between the ages of 6 and 12 years who (1) have received clinical diagnoses of ASD including autistic disorder, PDD-NOS, Asperger's syndrome based on the DSM-IV diagnostic criteria by a child psychologist or psychiatrist with expertise in autism evaluation; (2) have a score equal to or above 18 on the SCQ; (3) meet criteria for either autism or autism spectrum classification by the ADOS; and (4) have a nonverbal IQ equal to or greater than 80.

Exclusion criteria for the ASD group: Children who (1) have neurological disorders (i.e., seizures, tumor, severe head injury, stroke, brain lesion or disease); (2) are not ambulatory; and (3) have significant visual or auditory sensory impairment.

Other considerations in ASD group: (1) Concurrent medication use: Children that have been maintained on a stable (3 months) regimen of psychoactive medication will be included in the study and information regarding medication status will be recorded for use in post-hoc analyses. (2) Formal Behavioral Intervention: Children currently enrolled in a formal behavioral intervention program (30 hours or greater per week, overseen by a licensed practitioner; e.g., ABA or EIBI) will be excluded. Children receiving less than 30 hours per week of a formal behavioral intervention will not be excluded provided they meet other inclusion/exclusion criteria. (3) Comorbid Psychiatric disorders: Children with comorbid psychiatric diagnoses (e.g., ADHD) also will not be excluded provided other inclusion/exclusion criteria are met. (4) Other forms of concurrent therapy: History of or current dietary, allied health (e.g., speech, OT) intervention will not be an exclusion criterion. *The decision to allow subjects on other forms of treatment into the study is based on the difficulty of recruiting medication-free and other intervention-free children with autism.*

Typically developing children (TD) group: Typically developing children will *not* have a diagnosis of autism spectrum disorder, intellectual and developmental disability, or any other psychiatric or neurological diagnosis. We will use the DISC-2.3 to verify our TD children do not have any psychiatric diagnosis. In addition, we will also administer the SCQ to verify our TD children do not have an autism phenotype. For this purpose, we will use a cut off score of 10. We will recruit typically developing children to reflect the gender ratio expected in the ASD group. In addition, these children will be matched on chronological age and level of intellectual functioning.

b. Sources of Materials: The sources of research material obtained from each human subject will be in the form of information gathered specifically for research purposes. This will include data from evaluations and assessments, behavioral rating scales and direct observations of behavior. To protect subjects' confidentiality, only authorized persons from the University of Florida, the sponsor (NIH), and the corresponding Institutional Review Boards will have the right to review research records. Confidentiality of those records will be protected to the extent permitted by law. Research records will be kept secured in a locked archive and will not be released without the subject's consent unless required by law or a court order. When the results of this research are published or presented at scientific meetings, identity of subjects will not be disclosed.

c. Potential Risks: The risks of participating in this project include the evaluations, being observed, and exposure to prompting and positive reinforcement procedures.

The major risk of the evaluations is that subjects may experience mild discomfort resulting from testing although we will build in breaks to prevent fatigue or stress. Some children may experience prompting as aversive although a graded series of prompts should prevent this.

2. ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and Informed Consent: We believe we have a significant population base from which to recruit research participants. Recruitment will take place through the UF-CARD, one of seven state-supported CARD programs in Florida. UF-CARD is administratively housed in the Department of Psychiatry and McKnight Brain Institute, and serves a geographical region of 14 counties. The Center serves both children and adults who have autism or related developmental disorders and has a current constituency of about 1600 individuals. The P.I., Dr. Lewis serves as Executive Director of CARD and Dr. Radonovich, a Co-Investigator on this project, devotes 20% effort to CARD activities. Additionally, the University of Florida Division of Child and Adolescent Psychiatry provides outpatient services to children with autism and their families. Assessments and evaluations are provided to approximately six new children and their families per month. Drs. Tucker and Kim, co-investigators on this application, provide such care. Dr. Tucker also serves as Chief of the Child and Adolescent Psychiatry Division. Typically developing children will be recruited by advertising in the community. We will also recruit siblings of ASD participants if they provide appropriate matches for specific children in the ASD group. Finally, Dr. Vollmer's program routinely receives requests for participation in behavioral research relating to autism.

All participants will be provided with the name and telephone number, of study personnel as well as the telephone number of the performance site's Institutional Review Board. Individuals will be told that their participation is voluntary, and refusal to participate will not affect current or future care or services. Data will be gathered from questionnaires from parents, and face-to-face interview with parents, as well as direct testing of the child. To maintain confidentiality, study-specific identifiers will be assigned to individuals in the study. Strict procedures will be employed to maintain the confidentiality of the data. Only the research staff will maintain linkage between the study identification number and the subjects' names. Project staff will maintain a list of participant names and linkage to study identifiers in a secured file cabinet in project office space.

Protection Against Risk: To minimize the risk of the child becoming stressed, we have made each of the tests take only short periods of time and have made them so that they lend themselves to the attention span and interests of young children with or without disabilities. The clinic space where we work with children is also designed to be child friendly – with carpeting, child-sized furniture, and appropriate toys – and the child will be allowed to access his/her parent(s) at any time. If the child clearly does not like one of the tests and cannot be easily redirected, we will stop the task and will try it again only if the child gives interested in continuing and no longer appears stressed. The child does not have to be able to complete all of the tasks involved in order to participate.

Effective screening and the psychiatric evaluation will rule out other psychiatric conditions that may prevent someone from participating in these studies. Once the subject enters the study, an experienced research team will closely follow him or her. The research team has developed considerable expertise in monitoring the safety of subjects participating in research studies. An experienced research psychiatrist is available 24 hours a day, 7 days a week. If at any point in the procedures symptoms become distressing or dangerous, subjects will be withdrawn from the study and, if necessary, treatment instituted.

This project will be conducted in compliance with research statutes outlined in the Health Insurance Portability and Accountability Act. Each participant will be assigned a unique identification number, and this number will be used to link all subsequent information collected. This file will be secured with password access, since it represents a direct link between the name and identification number of a participant. All paper files and data are kept in locked file cabinets to ensure confidentiality. The other procedures to ensure confidentiality follow the regulations and policies of the University of Florida and Shands Hospital. Data file archival and back-up will be performed on a regular basis.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Subjects with ASD participating in the proposed project will derive significant potential benefit from participation. One potential benefit that subjects might derive from entering this study is an extensive diagnostic assessment as well as detailed assessment of their restricted, repetitive behavior. In addition, participants with ASD will receive intensive intervention designed to overcome their restricted, inflexible

behavior by increasing more flexible and variable responding. All research procedures will be provided free of charge.

One potential benefit that typically developing subjects might derive from entering this study is identification of potential developmental problems. Otherwise typically developing children will likely not derive any direct benefit from participation in these studies.

The benefits to society are discussed below under the “Importance of the Knowledge Gained” section.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

The focus of this application is a clinically important and highly understudied problem in neurodevelopmental disorders in general and autism in specific. Our proposed strategy is to promote the development of flexibility and variability in functional activities. The proposed project will be among the first to target variability and flexibility as a goal of intervention. Establishing ways to assess variability and flexibility in daily activities and develop ways to increase variability and flexibility in responding will be of significant benefit to individuals with autism and their families. Application of such assessment and intervention procedures in children with autism promises to have significant generalizable effects on brain and behavioral development and should be directly applicable to assessment and intervention in other neurodevelopmental disorders.

5. DATA AND SAFETY MONITORING PLAN

Once a subject is enrolled into the study, continuous close monitoring will be conducted by the Principal Investigator in conjunction with the other investigators as well as the UF Institutional Review Board, through annual reports of progress and by immediate notification of serious and unexpected adverse events by the PI to the IRBs. This information, as well as any other unanticipated problems involving risks to subjects or others, will also be reported to the NIH Project Officer.

Inclusion of Women and Minorities

No person shall be excluded from participation in this research study on the basis of gender or ethnicity alone. However, autism occurs at a much higher rate in males than in females (4:1). Therefore, it is anticipated that there will be a larger number of male participants in this project. Every effort will be made to recruit and include minorities among the participants in this research study.

The individuals with ASD as well as the typically developing children will be recruited mainly from Alachua County, Florida, which includes Gainesville. The total population of Alachua County from 2007 is 241,364 and racial categories are comprised of 73.7% White persons, 19.5% Black or African-American persons, 5.7% Hispanic or Latino, 4.7% Asian or Pacific Islander persons, 0.3% American Indian and Alaska Native persons, and 1.8% persons reporting two or more races. Alachua County are comprised of 7.3% Persons of Hispanic or Latino origin and 67.1% White persons not Hispanic.

Recruitment will be done through the CARD service programs as well as through statewide mental health centers, public schools and diagnostic clinics. We will distribute recruitment information at community agencies specifically serving people in ethnic communities (e.g., local churches, support groups, day care centers, community centers) in both English and Spanish. In previous pilot studies and grant funded projects we have found several recruitment and retainment strategies to be useful such as payment to the families and a report summarizing findings which will be similarly conducted in this proposal.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Developing a novel treatment for restricted inflexible behavior

Total Planned Enrollment: 40

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	3	4
Not Hispanic or Latino	10	26	36
Ethnic Category: Total of All Subjects *	11	29	40
Racial Categories			
American Indian/Alaska Native	0	1	1
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	9	13
White	7	18	25
Racial Categories: Total of All Subjects *	11	29	40

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

Inclusion of Children

Children are the focus of this project, and so by design, children will be included in the study. For this project we will recruit children diagnosed with autism spectrum disorders (ASD) between the ages of 6 and 12 years who are higher functioning. For the studies subsumed under Aim 1 of the R21, typically developing children also will be asked to participate. These children will be matched to the ASD children on gender, age and level of intellectual functioning. Our rationale for recruiting in this age and IQ range is to allow us to match ASD children with typically developing children on level of cognitive functioning. In addition, the involvement of somewhat older, higher functioning children will increase the feasibility of developing and testing our proposed intervention. Every effort will be made to make the children as comfortable as possible throughout all phases of the study.

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Resource Sharing Plan(s)

(a) *Data Sharing Plan*: Research data from the proposed project will be shared in multiple ways. First, we will use the conventional academic mechanisms of presentation at local, national, and international scientific meetings. In addition, we will submit our data for publication to peer-reviewed scientific journals in our field. Once our findings have undergone acceptable peer review and publication, we will follow the NIH Public Access Policy to ensure that the public has access to the published results of our NIH funded research. Finally, following publication we will share our findings with members the autism community and make our de-identified data available to other investigators if appropriate.

(b) *Sharing Model Organisms*: n/a

(c) *Genome-Wide Association Studies (GWAS): n/a*

PHS 398 Checklist

OMB Number: 0925-0001

1. Application Type:

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

* Type of Application:

☐ New ☒ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

Federal Identifier: MH091554

2. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

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

☐ Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes ☐ No ☐

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

* Previously Reported: Yes ☐ No ☐

Tracking Number:GRANT10655481 Funding Opportunity Number:PA-10-069 Received Date:2010-07-16T09:31:46-04:00

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)

5. * Disclosure Permission Statement

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

☒ Yes ☐ No