ASSESSING THE MALLEABILITY OF SPATIAL ABILITIES IN INDIVIDUALS WITH DOWN SYNDROME

NCT05332912

Initial IRB Approval: 9.19.2019

Lastest IRB Approval: 8.08.2024

PROTOCOL AND DATA ANALYSIS PLAN

Protocol Title:	Assessing the Malleability of Spatial Abilities in Individuals with Down Syndrome
Protocol Status:	APPROVED
Date Submitted:	07/15/2024
Approval Period:	08/08/2024-01/01/2050
Important Note:	This Print View may not reflect all comments and contingencies for approval. Please check the comments section of the online protocol. Questions that appear to not have been answered may not have been required for this submission. Please see the system application for more details.

*** * * Continuing Review * * ***

Continuing Review/Annual Report

WHAT TO UPLOAD WITH YOUR CONTINUING REVIEW APPLICATION

For studies where research activities are limited to data analysis, upload participant safety information and publications (e.g., manuscripts, abstracts) since the last IRB approval, if applicable.

For all other studies, upload:

- â€¢ A clean (unstamped) copy of consent/assent document(s) to be stamped upon IRB approval.
- â€¢ Participant safety information including the most current Summary of all serious adverse events and unanticipated problems involving NSKS to participants or other and data safety monitoring reports since the last IRB approval, if applicable.
- Any publications (e.g., manuscripts, abstracts) since the last IRB approval.

Any changes, updated and/or new study materials should be uploaded and questions 19 - 24 of this form should be completed.

1. **Please indicate the status of the study:**

a) The study has not started but will become active.
Please explain why the study has not started.

b) X The study is ACTIVE (please check the appropriate box below):
Study is open to accrual.
Study is on hold or halted.

Please explain what needs to occur before accrual can resume:

X Study is permanently closed to accrual.

i. Y Have all participants completed all research related activities/interventions?

ii. N/A Will the research only remain active for long-term follow-up of participants?

iii. Y Are remaining research activities limited to data analysis only?

For IRB office use: * may qualify for expedited review

c) The study has expired and needs to be re-initiated.

Explain any research activities occurring during lapse in IRB approval.

2. Date the study was initially approved by the IRB: 09/19/2019

3. Approval date of previous continuing review: 09/27/2023

4. Total number of participants/records/specimens approved to date. 102 (54 Children and 48 Down syndrome)

5. Total number of participants that have given consent (verbal or written) to date. 54 children and 30 Down Syndrome

6. Total number of participants that failed screening(if not applicable, state N/A). N/A

7. Total number of participants accrued since the beginning of the project. 84

8. For multi-center studies, number of participants approved for accrual study-wide (University of Alabama site plus all other sites). 102

9. For multi-center studies, number of participants enrolled study-wide (University of Alabama site plus other sites). 84

10. Number of withdrawals from the research (since last approval date) and explanation/reasons for withdrawals.

0

11. Description and number of:

a) Reportable Protocol Deviations/Violations since the last approval date:

0

b) Serious Adverse Events (SAEs) or unanticipated problems involving risks to participant or others since the last approval date:

0

12. Have there been any complaints about the research during the last year? N
If yes, please describe.

13. Briefly describe the progress of the study to date.
Data collection has been completed. Anaysis is underway.

14. Is there a Data Safety Monitoring (DSM) plan for this study?

X No
Yes, a copy of the DSM report(s) for the last approval period is attached.
Yes, but a copy of the DSM report(s) for the last approval period is not attached. Please explain below.

15. FDA Regulated Studies

Is this a Food and Drug Administration (FDA) Regulated Study, (i.e., involves drugs, devices, biologics)? If yes, please answer the following questions: N

a) Have there been any changes in the FDA status of any drug or device used in the study?
If yes, please explain:

b) Have any of the investigational drugs or devices used in this study received FDA approval?
If yes, please explain:

c) Have any new alternative drugs or devices been approved for treatment of the study condition that may affect participants willingness to participate?

If yes, please explain:

Have current participants been notified? Please explain:

d) Has there been a change in the standard care that may be considered as an alternative to the investigational drug or device or that would affect the original study design?

If yes, please explain:

Have current participants been notified? Please explain:

e) Is there any new information that might affect the risk/benefit ratio and the willingness of current study participants to participate or to continue to participate in the research?

If yes, please explain:

Have current participants been notified? Please explain:

f) Is there any new information about study as a whole, the drug, or device that needs to be provided to past participants

If yes, please explain:

If no, please explain:

g) Does the study include an investigator's brochure (IB)?

If yes, what is the current version date?

(If study has multiple IBs, attach current versions in Attachments section (#15))

16. Provide a summary of any recent findings, literature, or other relevant information

(especially pertaining to risks), if applicable.

N/A

17. Have there been any significant amendments or revisions to the protocol that the IRB approved during the past approval period? (Significant amendments include changes in study design or risk level including those that resulted in a change in consent). N

If yes, please briefly summarize the changes:

18. Are any changes (amendments) requested with this Continuing Review?

Y Yes, please complete the remainder of this form.

No, form is complete. Please submit.

19. Summarize the proposed changes to the protocol in lay terms including the type of change AND what the change involves.

Beverly Roskos, Alezandra Knapp, Ashley Kennedy, Karima Elgamal, Komal Kehra, Melinda Mo, Crystal Infante, and Joselyn Angon-Martinez have left the research program.

20. Provide justification/explanation for the proposed changes.

Researchers graduated or left because testing of participants has been complete.

21. Will currently accrued participants need to be notified of changes? N

If No, please justify why not.

Not relevant to past participants.

If Yes, please explain how AND when notification or re-consenting will occur.

Proceed to the appropriate section(s) of the electronic application and make your changes. Also make necessary changes in the protocol, Consent Form(s), Assent Form(s), Recruitment Statement, Questionnaire or other attachments, if applicable. Upload any affected IRB materials needing revision. Please provide the entire revised document (not just revised pages). Use track changes in uploaded documents being revised. Please upload a clean copy of each revised document to be stamped upon IRB approval.

NOTE: Protocol amendments must receive IRB review and approval before they are implemented, unless an immediate change is necessary to eliminate an apparent hazard to the participants.

Sponsored Studies: Remember to update the Sponsor's Protocol version number and date in the Funding section of the protocol.

Expedited Review

Attachments

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* * * Personnel Information * * *

Study Personnel Roles:
-Principal Investigator: accepts responsibility for study, can edit protocol, must submit to IRB
-Administrative Contact: additional study contact, can edit/prepare protocol, may or may not also be member of research team
-Key Personnel (Research Team): University of Alabama member of research team, can view protocol (not edit)
-Non-Alabama Collaborator: member of research team from another institution or organization outside of University of Alabama, has no access to system, must be provided with PDF of protocol.
-Department Chair: Official Department Chair, may or may not also be a member of research team, can view the protocol (not edit). NOTE: a proxy may be listed if the Chair is the PI.

IMPORTANT NOTE: Human Participants Protection Training is mandatory for all research team personnel.

Principal Investigator Mandatory

PI must be University of Alabama affiliate.

Name of Principal Investigator (Faculty, Staff or Student)	Degree (MD/PhD/Other)	Title
Merrill, Edward	PhD	Professor Emeritus

Email	Phone	Fax
emerrill@ua.edu	+1 205 200 2183	

Department Name

Psychology

Please indicate your status	Faculty
Is the (Role) also a Department Chair?	N
Human Subjects Training Completed?	Y

If you have completed training that is not auto-populated below, upload a copy in the Attachments section.

Research Team Member Duties Picklist

1.	X	Recruitment	2.	X	Obtains consent
3.	X	Determine participant Eligibility for Accrual	4a.		Participant Physical Examinations
4b.		Follow-up Visits including physical assessments	5.		Perform study procedures or Specimen Collection
6a.		Administer and/or Dispense Study Drugs, Biologics or Devices	6b.		Receive, Store, Manipulate or Account for Study Drugs, Biologics or Devices
7.	X	Participant Randomization or Registry	8.	X	Collection of Participant Data
9.	X	Report Data (CRFs, e-CRFs, Spreadsheets)	10.	X	Data Analysis
11a.	X	Review Adverse Events	11b.	X	Treat and Classify Adverse Events
12.		Other (Please insert explanation below.)			

Course	CourseCompletionDate	CourseExpirationDate	CourseID
Human Research	10/26/2008 5:53:42 PM	10/26/2010 5:53:42 PM	Medical Research
Human Research	5/8/2021 1:06:50 PM	5/7/2024 1:06:50 PM	Medical Research
CITI Conflicts of Interest	7/1/2022 4:27:17 PM	6/30/2026 4:27:17 PM	Conflicts of Interest
Human Research	7/1/2022 5:40:48 PM	6/30/2025 5:40:48 PM	Non-Medical Investigators
Human Research	7/16/2012 10:37:16 AM	7/16/2014 10:37:16 AM	Non-Medical Investigators
Human Research	7/17/2019 10:02:41 AM	7/16/2022 10:02:41 AM	Non-Medical Investigators
Responsible Conduct of Research	7/29/2010 10:52:43 PM	7/29/2014	Biomedical Responsible Conduct of Research
Human Research	7/29/2010 11:33:27 PM	7/29/2013	Medical Research
CITI Conflicts of Interest	7/5/2017 3:24:01 PM	7/4/2021 3:24:01 PM	Conflicts of Interest
Human Research	8/13/2014 9:47:52 PM	8/12/2016 9:47:52 PM	Non-Medical Investigators
Human Research	8/17/2016 2:10:40 PM	8/17/2019	Non-Medical Investigators

Key Personnel (Research Team)

Name of Key Personnel (Research Team)	Degree (MD/PhD/Other)	Title	Department Name
Bui, Chuong		Research Statistician	Alabama Life Research Institute
Conners, Frances		Professor	Psychology

Non - Alabama Collaborator

Name of Non - Alabama Collaborator	Degree (MD/PhD/Other)	Title	Department Name
Yang, Yingying	PhD	Assistant Professor	A&S
Samantha Zakrzewski		Undergraduate Research Assistant	Other
Stephanie Grinshpun	BA	Graduate Research Assistant	Other
Matthew Baker		Undergraduate Research Assistant	Other

Department Chair Mandatory

The official Department Chair should be listed here. If the Department Chair is the PI, a proxy may be listed.

Name of Department Chair	Degree (MD/PhD/Other)	Title
Davis, Thompson		New Faculty-PA Not Receive

Email	Phone	Fax
tedavis10@ua.edu		

Department Name

Psychology

Human Subjects Training Completed? Y

If you have completed training that is not auto-populated below, upload a copy in the Attachments section.

Is Chair a member of the study team? N

Research Team Member Duties Picklist

1.	Recruitment	2.	Obtains consent
3.	Determine Participant Eligibility for Accrual	4a.	Participant Physical Examinations
4b.	Follow-up Visits including physical assessments	5.	Perform study procedures or Specimen Collection
6a.	Administer and/or Dispense Study Drugs, Biologics or Devices	6b.	Receive, Store, Manipulate or Account for Study Drugs, Biologics or Devices
7.	Participant Randomization or Registry	8.	Collection of Participant Data
9.	Report Data (CRFs, e-CRFs, Spreadsheets)	10.	Data Analysis
11a.	Review Adverse Events	11b.	Treat and Classify Adverse Events
12.	Other (Please insert explanation below.)		

No training data is available.

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* * * Subject Population * * *

Subject Population(s) Checklist

Select All That Apply:

- [ ] Adult Volunteers
- [X] Cognitively Impaired Participants
- [ ] Employees
- [ ] Fetuses
- [X] Minors (under 18)
- [ ] Pregnant Women

Prisoners

Students (Note: If students will be compensated extra-credit or course credit for participation in the research, they must be given a non-research alternative for obtaining the same amount of credit, which is of comparable time and effort as is required by the research activity.)

Terminally Ill Participants

Wards of the State (Note: Please consider whether the research population may also be considered "prisoners" or "cognitively impaired." If so, please mark the appropriate corresponding categories in the Subject Population Checklist)

Non-English Speakers (Note: Please provide copies of all correspondence that will be used as a part of the research in English as well as in the native language of participants. Please also attach a copy of the Translator's Declaration.)

Other (any population that is not specified above)

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* * * Study Location * * *

Study Location(s) Checklist

Indicate where the study will be conducted. Select all that apply:

X	The University of Alabama	
X	Another University or College	Montclair State University, NJ
	VA Center	
	Hospital	
X	Other	Participant Home or Locations Selected by Parent

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* * * General Checklist * * *

General Checklist

Select All That Apply :

	Study Eligible for Exempt Review
	Non-human participants research
	Collection of Specimens
	Data collection via e-mail or the Internet
	FDA Approved Device
	FDA approved drugs, reagents, other chemicals administered to participants (even if they are not being studied), or biologic products
	Genetic Testing
	HIV Testing
	Human blood, cells, tissues, or body fluids
	Investigational drugs, reagents, chemicals, or biologic products
	Investigational Device
X	Investigator Initiated Study
	Medical Records
	Photography, Video, or Voice-Recording Participants
X	Questionnaires and/or tests
	Radioisotopes/radiation-producing machines, even if standard of care
	rDNA/Gene Transfer Therapy

Registry or Repository Creation
Specimens to be stored for future research projects (must be in consent form)
Study of existing data or specimens
Other (clarify in text box to the right)

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* * * Funding * * *

Funding Checklist

NONE

Funding - Grants/Contracts

Funding Type	Funded By
Government	National Institute of Health

NOTE: Applicable grant application, contract or subcontract, investigator's brochure, and sponsor's protocol (for all industry sponsored clinical trials) must be attached. Click "Add" to attach the documents.

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* * * Expedited Review * * *

PLEASE READ: For Expedited Review, all aspects of the research must include activities that (1) present no more than minimal risk to human subjects, and (2) involve one or more of the specific categories listed below.

Select the following applicable categories to determine if your research project qualifies under Expedited Review. If none of the categories are applicable to your research project, a Full Committee Review will be required. For Expedited or Full Review, proceed to complete the following application.If none of the expedited criteria are appropriate for your project, please move to the next screen WITHOUT checking any of these criteria; your protocol will be reviewed by the full IRB. Note: The IRB will make the final determination if your protocol is eligible for expedited review.

Select one or more of the following paragraph(s):

1. **Clinical studies of drugs and medical devices only when condition (a) and (b) are met.**
   a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
   b) Research on medical devices for which
      i) An investigational device exemption application (21 CFR Part 812) is not required; or
      ii) The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. **Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:**
   a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or
   b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and

collection may not occur more frequently than 2 times per week.

3. **Prospective collection of biological specimens for research purposes by non-invasive means.**

   Examples:

   a) Hair and nail clippings in a non-disfiguring manner;

   b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

   c) Permanent teeth if routine patient care indicates a need for extraction;

   d) Excreta and external secretions (including sweat);

   e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

   f) Placenta removed at delivery;

   g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

   h) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

   i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

   j) Sputum collected after saline mist nebulization.

4. **Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)**

   Examples:

   a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

   b) Weighing or testing sensory acuity;

   c) Magnetic resonance imaging;

   d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

   e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. **Research involving materials (data, documents, records, or specimen) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this paragraph may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)**

6. **Collection of data from voice, video, digital, or image recordings made for research purposes.**

7. **Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation,**

human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects - 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

X 8. Continuing review of research previously approved by the IRB as follows:

a) Research permanently closed to enrollment of new subjects, all subjects have completed all interventions, and research remains active only for long term follow up of subjects.

b) Where no subjects have been enrolled and no additional risks have been identified

c) Where remaining research activities are limited to data analysis

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two through eight do not apply but the IRB has previously determined that the research involves no greater than minimal risk and no additional risks have been identified.

*** * * Background , Purpose , Study Procedures * * ***

Study Title

Assessing the Malleability of Spatial Abilities in Individuals with Down Syndrome

Complete Sections 1 - 15. Specify N/A as appropriate. Do not leave any required sections blank.

1) Background

a) Describe past experimental and/or clinical findings leading to the formulation of the study, if applicable.

Spatial ability is one of three categories of basic abilities, along with verbal and quantitative abilities, that are the basis for developing many important independent living skills (Park, Lubinski, & Benbow, 2000). Verbal and quantitative abilities are prominently featured in school curriculum and assessments, whereas spatial ability has often been completely overlooked or received only limited attention. According to the National Academy of Sciences (2006) ”skill in spatial thinking is presumed throughout the K – 12 curriculum, but is formally and systematically taught nowhere.” Little appears to have changed in the past 13 years. Hence, there is heavy reliance on input from general experience rather than directed training to produce facility with spatial abilities and skills in TD children (Halpern, 2013; Newcombe & Huttenlocher, 2003). Several researchers have indicated that neglecting the importance of spatial ability can have widespread consequences for typically developing (TD) children and adolescents (Wai, Lubinski, & Benbow, 2009). However, the discussion of the importance of spatial ability for TD children tends to be focused on promoting interest and competence in STEM careers (Wai et al., 2009). We argue here that spatial ability plays a more basic role in the everyday functioning of persons with DS. Indeed, spatial abilities have direct applications to daily life, ranging from activities such as tying shoes to using hand tools and navigating the environment. They also serve as a cognitive foundation for many other complex skills such as solving mathematical problems and using spatial language. Moreover, they are used in many specialty jobs such as grocery stocking, packaging, and assembling, which are among the most commonly reported jobs for adults with DS. We believe that the study of spatial abilities in people with DS is necessary to minimize potential negative effects on basic daily functions, independent living skills, and job possibilities. In previous research we have reported difficulties in skills such as wayfinding that are particularly severe for persons with DS. We have also observed difficulties in utilizing the specific spatial abilities of mental rotation and perspective taking. The research proposed in this application stems from observations that spatial abilities are relatively easy to modify by increased experience with tasks that use spatial abilities in TD children

and young adults (Uttal et al, 2013). Therefore, providing additional and intentional opportunities to experience spatial tasks may be an important step in developing methods for improving performance in spatial skills in persons with DS.

b) **Describe any animal experimentation and findings leading to the formulation of the study, if there is no supporting human data.**

N/A

2) Purpose of the study

a) **Provide a brief lay summary of the project in <200 words. The lay summary should be readily understandable to the general public.**

Based on available literature and our own preliminary research, we have concluded that persons with Down syndrome (DS) exhibit difficulties in utilizing the specific spatial abilities of mental rotation and perspective taking, and performing complex spatial tasks such as wayfinding and environmental learning. A weakness in spatial abilities may have many direct applications to daily life, ranging from activities such as tying shoes to using hand tools and navigating the environment. They also serve as a cognitive foundation for many other complex skills such as solving mathematical problems and using spatial language for giving and receiving directions. Moreover, they are used in a variety of specialty jobs such as grocery stocking, packaging, and assembling, which are among the most commonly reported jobs for adults with DS. Hence, a new focus on spatial ability and its modifiability in persons with DS is clearly warranted. The primary goal of the research proposed in this application is to evaluate the malleability of mental rotation and perspective taking in people with DS through providing intentional experience with numerous spatial activities. Two groups of participants will be tested over the course of the project: adolescents and young adults with DS and typically developing children. Following an initial evaluation of performance on the two abilities, participants will receive up to eight sessions of spatial activity experience utilizing puzzle construction, block building, and computer search tasks. Following the experience sessions they will be re-evaluated. These data will be used to investigate two specific aims. First, we investigate whether spatial abilities of persons with DS can be modified by experience with spatial activities. Second, we investigate whether the degree of modification observed for persons with DS can reduce performance differences between them and TD children. We also consider whether performance on the PPVT, KBIT matrices, and Chronological Age are associated with any benefits from spatial ability experience. To the best of our knowledge, this is the first study to use experience with spatial activities to improve spatial ability functioning in persons with DS, or persons with intellectual/developmental disabilities in general for that matter.

b) **List your research objectives (specific aims & hypotheses of the study).**

Specific Aim 1: The first specific aim is to demonstrate that spatial abilities are malleable in persons with DS. Uttal et al. (2013) conducted a meta-analysis on more than 200 spatial intervention studies in individuals of all ages demonstrating that abilities are highly malleable and that even limited experience in spatial tasks can produce positive and lasting effects in TD children and adults. Indeed, numerous studies have shown that spatial ability performance of TD children and adults can be achieved by providing experience with tasks that utilize spatial abilities and do not require direct instruction (e.g., block play and puzzle construction). It is reasonable to expect that these results will generalize to persons with DS. However, this needs to be empirically evaluated. Hence, one important goal of the proposed research is to demonstrate that experience with spatial tasks can promote improvement in two specific spatial abilities (mental rotation and perspective taking) in persons with DS. To test this specific aim, we will compare spatial ability performance of persons with DS before and after varying levels of experience with spatial activities.

Specific Aim 2: The second specific aim is to evaluate whether persons with DS and TD children matched on nonverbal ability exhibit the same degree of improvement as a function of similar experience with spatial abilities. If persons with DS exhibit greater improvement than TD children, then it may be that the weaknesses observed in spatial abilities reflect a lack of opportunity to engage in spatial ability experience. If, on the other hand, persons with DS exhibit less improvement, it may be that weaknesses observed in spatial abilities reflect a lesser ability to benefit from intentional experiences. In the proposed research, we will also evaluate the relations between degree of improvement and measures of Nonverbal ability, Receptive Language, and Chronological Age to identify differences in how these variables contribute to performance improvements in the two groups. The results of these analyses may also help to identify persons with DS who are most likely to benefit from spatial ability experience to promote improvements in spatial abilities.

c) Describe the study design (e.g., single/double blind, parallel, crossover, control, experimental, observational, etc.)

N/A
Single blind
Double blind
Parallel
Crossover
X Control group
X Experimental group
Observational
X Other

Mixed Design (Between/Within Subjects) Pre-test/Post-test Comparison

d) Provide a timeline for individual participant recruitment and follow-up (analysis for the study is required).

Participants will be recruited from various sources including the UA Participant Registry, DS Connect (NIH Registry of individuals with Down syndrome interested in research), local schools, and local service providers. Following initial contact by these various sources, participant families will self-identify to receive additional information about the study - including a copy of the Parental Consent. The study will take place over the course of 4 months for each participant, All participants will receive the PPVT, the KBIT 2 Matrices subtest, an assessment of Mental Rotation, and an assessment of Visual Perspective Taking during the first testing session (Approximately 45 minutes). Mental Rotation and Perspective Taking performance will be assessed two additional times for all participants, once following Experience Session 16 and once following Experience Session 32. These two assessments will take approximately 15 minutes. Experience sessions will be provided twice per week, with each session lasting approximately 30 minutes over a period of 16 weeks. Half of each group (No Delay participants) will begin spatial ability experience during a first experience session scheduled approximately one week following the initial assessment. The other half of each group (Delay participants) will not begin the spatial ability experience for the 8 weeks following the first assessment and serve as a control for practice effects on the assessment measures. The Delay participants will receive a second assessment on the Spatial Abilities and begin spatial ability experience during week 9. They will receive the same protocol as the experimental participants following the second assessment (8 weeks experience, ability assessment, 8 weeks experience, ability assessment). The final assessment will come following Experience Session 32 (week 16). Data analysis is planned upon the completion of all data collection during year 03 of the

project period.

e) **Will participant be randomized?** Y

f) **If participants will be given placebo, please justify placebo use, and describe contents of the placebo.**

NA

3) Study Procedures

a) **Is this project a multicenter study (i.e., same project is conducted elsewhere by a different investigator)?** Y

Is University of Alabama acting as a coordinating center for other sites? Y

Will the University of Alabama site be participating in all parts/procedures/arms of the study? Y

If No, explain what University of Alabama will NOT participate in:

b) **Describe all the procedures, from screening through end-of-study, that the human participant must undergo in the research project, including study visits, drug treatments, randomization and the procedures that are part of standard of care. Specify which procedures are for research and which are standard of care. If study involves only retrospective record review, describe that review process here, including how records will be selected for review. Please note: The box below is for text only. If you would like to add tables, charts, etc., Click "Add" to attach the documents.**

Due to CoVid Restrictions, Procedures were adapted for online presentation via Zoom. Ravens and PPVT-4 used available commercial formats. Mental Rotation and Perspective Taking involved the creation of Video presentations. Online presention was approved by the University IRB on 03/04/2020.

The initial assessment will include four measures:

Ravens 2 Matrices: The Ravens 2 Matrices is a 60 item measure of nonverbal ability. The subtest measures a participant's ability to solve problems, identify relationships, and complete visual analogies without testing language skill. The examiner shows the participant pictures or abstract designs that follow a pattern, with one element missing. The participant is instructed to point to a picture that will complete the pattern. Participants will be matched on raw score performance. Completing the subtest should take less than 15 minutes for most participants.

PPVT-4: The PPVT – 4 is a norm-referenced test for measuring receptive vocabulary of children and adults. The test is administered individually. Each item consists of four colored pictures that serve as response choices on each page. For each item, the examiner says a word and the examinee selects the picture option that best represents the word's meaning. The test is normed for 2 years, 6 months to 90 years. Average time to administer the test is 10 – 15 minutes.

Mental Rotation Assessment - On each trial, participants will be presented a geometric shape (e.g., a block letter L) in the center of a computer screen that completes one of two rectangles presented at the bottom of the same screen. The open area in one rectangle is the mirror image of the open area in the second rectangle. The shape in the center of the screen will fit one of the rectangles when horizontal. The shape can be rotated from horizontal by 0, 45, 90, 135, 180, 225, 270, or 315 degrees. Participants respond by touching the rectangle into which the shape will fit once oriented properly (using touchscreen technology). Participants receive 4 trials at each orientation.

Perspective Taking - Participants will be seated at a table with four chairs and four different objects (street lamp, mailbox, stop sign, traffic signal) representing each location on the corner of a city block in front of each chair. A stuffed animal is placed behind each object. One experimenter walks around the table stopping at each location. At each location, the participant is told that the experimenter is taking a picture from that location and he/she is asked to look at four pictures. The task is to select the picture that the experimenter has just taken. The four pictures consist of the participant's point of view, a mirror image of the participant's point of view, the experimenter's point of view, and a mirror image of the experimenter's

point of view. This task will take 5 - 10 minutes.

Assessments 2 and 3 will include only Mental Rotation and Perspective Taking Assessments.

Spatial Ability Experience will include two tasks of Object manipulation and two Large Environment Experiences. These tasks are meant to provide experience.

Object Manipulation Experience: Two categories of tasks will be used to provide object manipulation experience: LEGO Block Play and Puzzle Construction. One task will be used in each spatial ability experience, with tasks alternating between sessions.

LEGO Block Play: Participants and experimenter will each have 20 multi-colored and multi-shaped connecting blocks. During play, the participant and experimenter will alternate creating structures and copying what the other has created during the 15 minute interval. No specific corrective feedback will be given during the experience, although participants will be asked if they think their construction matches the model. Object manipulation rather than accuracy is the basis of the experience. Participants will be allowed to take as long as they need to complete their copy of each structure.

Puzzle Construction: We will select puzzles that include 4, 8, 12, 16, or 20 puzzle pieces. All puzzles will have pieces that need to be rotated to fit the puzzle board to provide the necessary object manipulation experience. The puzzle board will also include the outline of the shapes of the pieces. Hence, participants will need to match the outline of the piece with the rotated actual piece to efficiently complete the puzzle. Touching each piece with a finger will rotate the piece, and removing the finger will stop the rotation. Participants will be given five puzzles to complete during the experience session. They will be given 3 minutes to complete each puzzle. If they complete the puzzle, they will receive the next larger size puzzle for their next opportunity. If they fail to complete the puzzle, the size of the puzzle will be reduced by one level.

Large Environment Experience: Two categories of tasks using a large scale virtual environment will be used to provide object manipulation experience: Hide and Seek and Wayfinding. One task will be used in each spatial ability experience, with tasks alternating between sessions.

Hide and Seek Video Game: The setting will consist of a classroom with four different color doorways. The participant will be identified as an avatar (self-selected) in the center of the classroom. A second avatar will represent a person hiding behind one of the doors. The doors will be described as “see through” from the perspective of the hiding avatar. The participant will be shown a panoramic view of the classroom. Then he or she will be shown the view from the hiding avatar. The view will return as the point of view of the participant avatar and the participant will be instructed to find the door that the second avatar is hiding behind. The participant will be allowed to look behind any door to find the hiding avatar. If the participant selects the wrong door, they will be shown the view of the hiding avatar again and asked to continue the search. Once found, the avatar will be placed behind a second door and the procedure will be repeated. There will be four trails per session.The experimenter will record the number of wrong locations that were searched and the time to find the hiding avatar for each search event. Time for this task will be approximately 15 minutes.

Wayfinding Video Game: We will introduce the participant to an environment (e.g., a shopping mall) and allow them to explore the environment looking at the different stores and items in the stores for 5 minutes. We will then ask them to shop for particular items in the various stores. For each item, they will need to start from a different location in the mall (i.e., the shop in which they made their last purchase). Hence, to make a correct initial choice of a turn when leaving the store, participants will need to be able to reconstruct their environment from a different perspective. We will ask them to locate up to 5 items for a maximum of 10 additional minutes. The experimenter will record whether or not the participant made a correct initial turn choice leaving the starting point, how long it took to get the correct item location, and how many items they had time to locate during the session. Total time will be 15 minutes.

We are seeking permission from participants to record the ZOOM feed of participant performance on the Spatial Ability and Verbal Ability tasks.

c) **Provide stopping rules for the study, If the proposed study is a clinical trial where a drug, vaccine, device or other treatment is compared to a placebo group or comparison treatment group, what are the guidelines or endpoints by which early decisions regarding efficacy or lack of efficacy can be made? For example, it may be reasonable to stop enrollment on a study when efficacy has already been clearly demonstrated, to avoid unnecessary enrollments of additional participants. Alternatively, it may be reasonable to stop enrollment when it is clear that efficacy will never be demonstrated, given the statistical power of the study as designed. Describe the guidelines that are in place to assist in making these determinations, if relevant to the proposed study.**

NA

d) **Describe how data analysis will be performed (statistical tests, methods of evaluating data) and indicate the smallest group/unit for which separate reporting will occur. For studies involving a questionnaire, if data and reliability information are available, please describe or provide references. (Page numbers from a sponsor's protocol/grant may be referenced in this section).**

The independent variables of interest will be Group (DS and TD), Delay (No Delay and Delay), and Assessment (1, 2, and 3). The smallest number of participants in any given cell of the design is 20 participants.

Specific Aim 1 evaluates the malleability of MR and PT performance in participants with DS. Consistent with Aim 1, we will apply Multivariate ANOVA to the subsample of DS children. If the test for sphericity is significant, we will interpret the multivariate tests for the within subject effects. If not, we will use the univariate tests due to their increased statistical power. With either option, the test for the effect of Assessment, if significant, would indicate that performance of the DS children improves over time. We will then evaluate the interaction of AssessmentDelay, which if significant would signify that Delay vs No Delay participants exhibit a different magnitude of improvement across Assessment times. One contrast of interest compares Delay vs No Delay participants at Assessment 2. Performance favoring the No Delay participants would indicate a significant effect of spatial ability experience. A second contrast of interest compares Assessment 3 performance to Assessments 1 and 2 for the Delay participants. If we are able to confirm that the Delay participants exhibit higher scores at Assessment 3 than at Assessments 1 and 2 (which should not differ) then the benefits of spatial ability experience for persons with DS would be further confirmed.

Specific Aim 2 evaluates possible differences in rate and magnitude of improvement of DS and TD participants. We will approach Aim 2 in a very similar statistical manner. For Aim 2a, we will apply Multivariate ANOVA to the whole sample to test for the effect of AssessmentGroup. If significant, it is indicative that DS and TD participants do not exhibit the same degree of improvement following training. If improvement in performance is greater for the participants with DS, it

would indicate that experience may be a primary contributor to initial differences in spatial abilities of the DS and TD participants. If improvements are greater for TD children or similar for both groups, it would suggest that initial differences in spatial abilities between groups are not solely due to differences in experience. We will also examine the interaction of Assessment Group Delay complemented with contrasts to explore more closely how participants with DS compare to TD children. For example, we will compare rate of change over Assessments to see if the participants with DS need more experience to reach the same level of performance as the TD children. This may indicate the need for more intensive training for participants with DS to modify spatial ability performance.

*** * * Radioisotopes or Radiation Machines * * ***

4) Radioisotopes or Radiation Machines

Please note: For projects requiring radiation procedures, please contact the UA Environmental Health and Safety Office at 348-6010

a) **If applicable, summarize in lay language the radiographic diagnostic and therapeutic procedures associated with this protocol. (X-ray, fluoroscopy, CT, radioactive materials, nuclear medicine, PET-CT, radiation oncology, accelerator, Cyber Knife procedures, etc.).**

b) **Are the radiation procedures being performed a normal part of the clinical management for the medical condition that is under study (Standard of Care), or are the procedures being performed because the research participant is participating in this project (extra CT scans, more fluoroscopy time, additional Nuclear Medicine Studies, etc.) (Not Standard of Care)? If some procedures are Standard of Care and some are Not Standard of Care, check both boxes.**

NOT STANDARD OF CARE	STANDARD OF CARE
If it is not standard of care,complete the rest of this section. Provide the University of Alabama RSC approval information below.	If it is only standard of care, skip the rest of this section.

c) **Are research-related radiation procedures limited to X-rays only?**

Yes (Complete X-ray table).

No (Skip X-ray table).

d) **Total Radiation Exposure (in mRems) from x-ray procedures:**

To calculate radiation exposure from x-rays only, University of Alabama allows use of the Duke University Radiation Safety Committee dose estimate calculator. University of Alabama does not allow use of this website to calculate any other type of radiation exposure.

To determine the dose estimate, click on the appropriate links, below (you will be taken to the Duke University Radiation Safety Committee website). Enter the x-ray procedures into the appropriate fields of the website and click "create statement". Enter the dose estimate from the statement in the table above.

For studies involving adults, please click here.

For pediatric studies, please click here..

e) **Please list all radiation procedures (including x-ray) that are research-related (not standard of care). Include the anatomical location and specify the number of times that each procedure will be conducted throughout the entire study.**

NOTE: The IRB will determine if this study requires radiation safety review by the Radiation Safety Officer or the Radiation Safety Committee.

For more information on how to submit for radiation safety review, contact the Radiation Safety Officer.

*** * * Drugs, Reagents, Chemicals, or Biologic Products * * ***

5. Drugs, Reagents, Chemicals, or Biologic Products

Pilot	Phase I	Phase II
Phase III	Phase IV	Not Phased

a) Please list in the space below all investigational drugs, reagents or chemicals to be administered to participants during this study.

b) Please list in the space below all FDA approved drugs, reagents, chemicals to be administered to participants during this study.

Please read the IND Statement 1 and IND Statement 2.

*** * * Devices * * ***

6. Devices

a) Please list in the space below all investigational devices to be used on participants during this study.

b) Please list in the space below all FDA approved devices to be used on participants during this study.

*** * * Subject Population(a-h) * * ***

7. Subject Population - In the space below, please detail the participants that you are requesting to recruit (include description of each group requested)

a) Expected age range of participants. (For example - 19 yrs to 90 yrs).

Participants with Down syndrome will be between 10 and 30 years of age.

Typically developing children will be between 4 and 9 years of age.

We will test 48 participants per group - plus an additional 6 typically developing children as needed to provide a closer match on nonverbal ability for the children in the Experimental condition with the children in the control condition.

b)	i) Number to be directly solicited for this research.	X N/A	
	ii) Number to be consented (including withdrawals or screen failures)	N/A	102
	iii)Number expected to complete the study.		102
c)	If this is multi-center study, number of participants to complete the study study-wide	N/A	102
d)	If study involves review of medical or other records, number of records to be reviewed.	X N/A	

e) If women, minorities, or minors are excluded, a clear compelling rationale must be provided unless not applicable. Examples for not including minors: disease does not occur in children; drug or device would interfere with normal growth and development; etc.

NA

f) Describe how potential participants will be identified for recruitment (e.g., chart review, referral from individual's treating physician, those individuals answering an ad). How will potential participants learn about the research, and how will they be recruited (e.g., flyer, e-mail, web posting, telephone, etc.)? State where recruitment materials will be located. Click "Add" to upload recruitment materials document.

Important to remember: Study Activities cannot begin until IRB approval is granted.

General Information: Potential recruitment sites are identified and we provide them with information about the study. We ask them to identify potential participants and to send recruitment and consent information to the parents/guardians of the identified individuals. We do not get any identifying information on individuals at this point in time. Participants self-identify to the researchers by returning signed consent forms with contact information or by requesting additional information about the study. We will not contact any individuals who have not identified themselves as interested in the study. Information to be discussed with recruitment sites and a draft letter for them to send to parents/guardians is attached.

The University of Alabama participants with DS will be recruited from the University of Alabama Intellectual Disabilities Participant Registry that was established with NICHD Recovery Act Funding (Conners, PI). Participants will also be recruited through local DS organizations like DS Alabama, DS Connect, and through local public schools. Montclair State University participants with DS will be recruited from local service providers, DS Connect, and local public schools. The lead PI at Montclair State has established research relationships with these organization in the past several years. Twenty-four participants will be tested at UA and 24 at Montclair State University.

Typically developing children will be recruited from local preschools and elementary schools, including The University of Alabama Children's Program and the Montclair State University preschool program. Twenty-seven participants will be recruited from each site.

We have secured permission from the CDRC (see attached permission email) and recruited typically developing children from that site. We are adding the following organizations for recruitment and will be contacting them about recruitment following approval of the new recruitment materials. We will be identifying additional recruitment sites in the future that will be added to the list once contact is made.

https://childrenhelpingscience.com/
Massachusetts Down Syndrome Congress
Global Down Syndrome Organization
New Jersey Down Syndrome Organization

The new recruitment materials include Flyers and access to the PIs research web page. These are attached to the current protocol for review. Ed Merrill's research web page is visible for a short time if you would like to view it formatted. Organizations have not been invited to view the page prior to approval. The Web Page address is: https://emerrill.people.ua.edu/research.html

Letters of support from organizations assisting with recruiting efforts will be provided to the IRB. WE have attached an email approving recruitment from The University of Alabama CDRC.

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* * * Subject Population(i-l) * * *

7. Subject Population (continued)

i) Inclusion and Exclusion Criteria.

Identify inclusion criteria.

All participants must meet the following enrollment criteria based on parental report: (1) adequate vision for tasks in this study, (2) adequate verbal skills for understanding instructions for tasks, and (3) no accompanying diagnoses of Autism Spectrum Disorder as autism symptomology could confound results.

Identify exclusion criteria.

No additional exclusion criteria are established.

j) **Compensation. Explain the amount and schedule of compensation, if any, that will be paid for participation in the study. Include provisions for prorating payment.**

Participants will receive a Tablet computer (Valued at Approximately $75) and $100 for completing the study. If a participant cannot complete the study, they will receive payment at the rate of $25 dollars for starting each of the four months of the study.

If approved, we will be offering parents and parents to complete the project in less time by increasing the number of experience activities completed each week. If parents choose this option, they will be paid $25 for completing each 25% of the scheduled activities (4 experiences with each of the 4 activities).

k) **Describe who will cover study related costs. Explain any costs that will be charged to the participant.Include provisions for prorating payment.**

There are no costs to participants.

l) **Estimate the probable duration of the entire study including data analysis and publication. This estimate should include the total time each participant is to be involved and the duration the data about the participant is to be collected. If the study is Investigator-initiated, a timeline for individual participant recruitment, follow-up, total time for participant accrual, and data analysis for the study is required.**

Each participant will be enrolled for approximately 17 weeks following completion of the consent process. This translates into two sessions per week, with two experience activities per session. We now believe the activities will take approximately 10 minutes per session. (Participants will be recruited on a rolling schedule, with different participants recruited and tested throughout the duration of the study. Data collection for the study is projected to take approximately 3 years. Data analysis and publication should take place in the year following data collection - for a total time of 4 years.

Initial participants have inquired about the flexibility of this schedule. From a research integrity perspective, we believe it is feasible to conduct the study in less time per person if they are willing and able to complete additional experience activities during each week. We would like to provide participants with the option of completing up to twice as many activities during each week - reducing time to complete the study by half. This can be done by increasing the number of sessions per week or increasing the number of activities per session. Care will be taken to ensure that participants do not become fatigued during there sessions. We will complete no more than twice the activities in any given session, and no more than twice the number of sessions per week.

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* * * Subject Population(m) * * *

Research Involving Children

NOTE: Investigators, please include this information with the e-Protocol application if your research involves children. In Alabama a child is an individual less than 18 years of age unless the child is legally emancipated. If your research involves children with more than one vulnerability (e.g., children who are pregnant, incarcerated, or cognitively impaired) attach the supplementary information for that vulnerable population as well.

Minimal risk means that the probability and magnitude of the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life of a healthy child or during the performance of routine physical or psychological exams or tests.

Section 1.

Select and complete the category that applies to your research.

X Category 1 (45 CFR 46.404; 21 CFR 50.51)
My research does not involve greater than minimal risk.

a) My research falls under this category because:

My research involves research on individual or group characteristics or behavior (including perception, cognition, language, social behavior, etc.) or research employing survey, interview, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. The probability and magnitude of the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life of a healthy child or during the performance of routine physical or psychological exams or tests. No deception isinvolved.

b) Describe what provisions will be made for soliciting the assent of the children, and the permission of both parents, or the legal guardian. (Permission from both parents must be obtained unless one parent/guardian is deceased, unknown, incompetent, or not reasonably available, or when only one parent/guardian has legal responsibility for the care and custody of the child). Justify reason(s) if seeking permission from only one parent.

Parents will be sent information about the study and signed consent is required prior to asking children to participate. Children will be told about the study and will be included only if they assent to volunteer for the study.

We only plan to obtain signed consent from one parent for the following reasons. First, the study is minimal risk and only requires that participants engage in behaviors similar to those of their daily lives. Second, we do not have the means to firmly establish family status for families of participants to determine if both parents are available for consent. Third, and most importantly, the failure include participants of families without two parents available to consent will render the sample ungeneralizable to the population as a whole and have the likely and inadvertent effect of disproportionately eliminating potential participants from minority and lower SES groups.

Category 2 (45 CFR 46.405; 21 CFR 50.52)
My research involves greater than minimal risk but presents the prospect of direct benefit to the individual participants.

a) My research falls under this category because:

b) Justify the risk(s) by explaining the anticipated benefit to the participants:

c) Explain how the relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches:

d) Describe what provisions will be made for soliciting the assent of the children, and the permission of at least one parent/guardian. (Permission from both parents must be obtained unless one parent/guardian is deceased, unknown, incompetent, or not reasonably available, or when only one parent/guardian has legal responsibility for the care and custody of the child). Justify reason(s) if seeking permission from only one parent.

Category 3 (45 CFR 46.406; 21 CFR 50.53)
My research involves greater than minimal risk, and no prospect of direct benefit to individual participant, but likely to yield generalizable knowledge about the participant's disorder or condition.

a) My research falls under this category because:

b) Describe how the risks for participating in your research represent a minor increase over minimal risk (i.e., the children being recruited have a disorder or condition that would place them in a group other than an average healthy child; therefore, the research qualifies as a minor increment over minimal risk. This risk is slightly more than what the average healthy child would experience, but is reasonable for these participants because it is not more than they would experience or expect given their condition.).

c) Describe how the research intervention(s)/procedure(s) present experiences to participants that are reasonably commensurate to those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

d) Explain why the intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition, which is of vital importance for the understanding or amelioration of the participants' disorder or condition:

e) Describe what provisions will be made for soliciting the assent of the children, and the permission of both parents/guardians. (Permission from both parents must be obtained unless one parent/guardian is deceased, unknown, incompetent, or not reasonably available, or when only one parent/guardian has legal responsibility for the care and custody of the child). Justify reason(s) for seeking permission from only one parent.

Category 4 (45 CFR 46.407; 21 CFR 50.54)
My research does not fall under Category 1, 2, or 3 listed above. However, the research presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

(NOTE: If your research is funded by, or funding has been sought from the Department of Health and Human Services (DHHS), Department of Education, or is FDA regulated, a report must be sent for review to the DHHS Secretary, Secretary of the US Department of Education, or Commissioner of FDA. If this category is applicable, the Office of Research Compliance will prepare and submit a report of IRB review to the appropriate federal official(s)).

a) My research falls under this category because:

b) Describe what provisions will be made for soliciting the assent of the children, and the permission of both parents/guardians. (Permission from both parents must be obtained unless one parent/guardian is deceased, unknown, incompetent, or not reasonably available, or when only one parent/guardian has legal responsibility for the care and custody of the child). Justify reason(s) if seeking permission from only one parent.

Section 2.

In order to effectively assess and evaluate the risk of your proposed research to children, the IRB requires the following information. Respond to all items.

a) Provide justification for the participation of children as research participants in your study.

The children used in this study are necessary for providing a comparison group matched on non-verbal ability with participants with Down syndrome. In this type of research, it is necessary to evaluate the performance of individuals with Down syndrome against participants who are matched on general ability measures to determine if the difficulties associated with Down syndrome are beyond that which would be expected based on developmental level.

b) Has this research been conducted in adults? Y

If yes, is there any indication that the proposed research would benefit, or at least not be harmful to children?

Similar research has been conducted in adults and children with no adverse effects. The children are essential for providing a comparison group for the participants with Down syndrome.

c) Indicate how many children you propose to enroll in the study and justify this number (whenever possible, involve the fewest number of children necessary to obtain statistically significant data which will contribute to a meaningful analysis relative to the purpose of the study).

All of the typically developing participants will be children (48 participants originally planned). Many of the participants with Down syndrome will also be participants (we anticipate about half of the 48 participants in this group, or 24). The total number of participants was determined by power analysis. A 4 groups x 3 repetitions analysis with alpha set at .05, power set at .80, and total N = 96 (24 in each group) would be sufficient observe a significant effect size (f(V)) of .27 or greater. To evaluate the power for simple effects tests to compare the effects of training for the DS and TD participants separately, we conducted a 2 groups (Delay and No Delay) x 3 repetitions analysis with alpha set at .05, power set at .80, and total N = 48 (24 in each group). Power analysis indicated that 48 total participants would be sufficient to observe a significant effect for effect sizes (f(V) of .27 or greater for main effects of Delay and of .25 or greater for main effects of Assessment Time. Power calculations were conducted in GPower 3.1.9.2 (Faul et al., 2007). However, we are requesting and additional 6 typically developing participants at this time to make it possible to better match the Experimental and Control group children on nonverbal ability.

d) Describe how assent of a child will be obtained and documented (if applicable). If not applicable, explain why.

The different procedures will be described to the participant at the start of each session. They will then be asked if they want to take part in the current days activities. We will only continue if the participant agrees to continue. We will record whether or not assent was given on our daily record sheet before continuing on each day.

I am requesting waiver of the requirement for assent.

Justify:

OR

I have attached an assent form/assent script for IRB review. Y

e) Explain what methods will be used for evaluating dissent (i.e., description of behaviors that would indicate child does not want to participate (such as moving away, certain facial expressions, head movements, etc...).

If children indicate they do not want to perform the activities or appear reluctant to perform the activities by resisting, frowning, shaking their heads, etc.) we will discontinue the activities for the day. If they appear reluctant to continue for multiple sessions (i.e., two in a row without explanation) they will be discontinued from the study.

f) Describe how parental permission will be obtained. [Note: If you propose to waive the requirement for parental permission (i.e., getting parental permission may be against the best interest of the child, i.e., a study of abused or neglected children), describe what measures will be taken to protect the rights and welfare of the children.]

The study consent will be sent to parents and they will be asked to return it via mail or in person. They will be given the opportunity to call the PI to request additional information. Participants will be asked to be in the study only after a signed consent has been

returned to the experimenter.

I am requesting waiver of the requirement for parental permission.

Justify:

OR

I have attached a parental permission form for IRB review. Y

g) Describe measures that will be taken to ensure that a parent is present when the child participates in any research interventions or procedures. [Note: If the nature of the research is such that it is not appropriate to have a parent present (i.e., research into sensitive personal issues, physical examinations of teenagers, etc...) please explain why.]

Parents will be required to be in the home or on campus when their children are tested to ensure their presence in case of an emergency. If the parent cannot be present, testing will be rescheduled.

h) Describe the expertise of the research staff/study personnel for dealing with children at the ages included and whether they are knowledgeable and sensitive to the physical and psychological needs of the children and their families. Describe the appropriateness of facility in which the research will be conducted in relation to environment and/or equipment accommodating to children.

Drs. Merrill, Conners, and Yang have been conducting research with children for many years and are knowledgeable and sensitive to the needs of child participants and families. All Graduate and Undergraduate student Research Assistants will be trained by these faculty. Before they will be allowed to conduct the project on their own, they will participate in sessions with the faculty, and then observed by the faculty when they first take the lead role in conducting the sessions. Two RAs will be present during all testing sessions as an added measure to ensure that the needs of participants are met. We anticipate that most sessions will take place in the participants home. When taking part on campus, rest room facilities and a break area with approved snacks will be provided as needed.

i) If applicable, provide any additional information that may support your request to involve children in this research.

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* * * Subject Population(n) * * *

Research with cognitively impaired persons

NOTE: Investigators, please include this form with IRB application if your research involves cognitively impaired (decisionally impaired or decisionally challenged) persons. If your research involves people with more than one vulnerability, please complete the supplementary form for that population as well.

The IRB may ask you to designate an impartial observer to monitor the consent process or it may send its own representative to do so.

Section 1.

Note:Check the box next to the category that in your best judgment applies to your research, and provide the information requested in the space provided.

Note: Minimal risk means that the probability and magnitude of the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological exams or tests. (i.e., daily life of health persons)

X **Category 1**
My research does not involve greater than minimal risk.

Explain. If appropriate, describe what provisions are in place for allowing a Legally Authorized Representative (LAR) or other person with the participant's best interests at heart to assist the participant in navigating the research process:

We will require parental/guardian consent even if the participants with Down syndrome are adults. Adult participants with Down syndrome will also be required to sign a consent form.

Category 2
My research presents greater than minimal risk and prospect of direct benefit to the participants.

Explain. If appropriate, describe what provisions are in place for allowing a Legally Authorized Representative (LAR) or other person with the participant's best interests at heart to assist the participant in navigating the research process.

Category 3
My research presents greater than minimal risk and no prospect of direct benefit to the participants, but likely to yield generalizable knowledge about the participant's disorder or condition, because:

Explain. If appropriate, describe what provisions are in place for allowing a Legally Authorized Representative (LAR) or other person with the participant's best interests at heart to assist the participant in navigating the research process.

Category 4
My research does not fall under Category 1, 2, or 3, listed above.

If you check this category, the IRB determines additional safeguards on a case-by-case basis.

Section 2.

1. Explain why individuals with impaired decision-making capacity are suitable for this research. If the objective(s) of the study allow for inclusion of competent participants, provide compelling justification for inclusion of incompetent participants.

   The research has a primary goal of assessing malleability of spatial skills of persons with Down syndrome. These abilities are known to be deficient in Down syndrome and are particularly important in several aspects of daily functioning (e.g., navigation, work). Hence, it is necessary to evaluate whether or not these abilities are modifiable in persons with Down syndrome.

2. Describe who will determine individuals' competency to consent and the criteria to be used in determining competency (e.g., use of standardized measurements, consults with another qualified professional, etc...).

   Parents will provide the necessary consent for participation.

3. It should be recognized that decision-making capacity may fluctuate, requiring ongoing N assessment during the course of the research. Is it reasonable to expect that during the course of the research, subjects may lose their capacity to consent or their ability to withdraw?

   a) Describe what provisions are in place for periodic re-consent. Include the rationale and procedure, the proposed interval, any changes in behavior that might signal the need to re-consent whether or not the proposed interval has elapsed, and any consultative resources that are available for these decisions. Describe the process for re-consent or re-assent, or reassessment of willingness to continue participation.

   b) Describe what provisions are in place to protect the participants' rights in the event they lose their capacity to consent or their capacity to withdraw during the course of the research. (e.g., power of attorney, consent a caregiver as well as the patient, etc.).

c) Describe what provisions are in place for use of additional waiting periods to allow potential participants time to consult with family members about whether or not to participate.

4. Explain how you will identify who is authorized to give legally valid consent on behalf of any individual(s) determined to be incapable of consenting on their own behalf.

Our approach to consent to participate will include two steps. First, initial contact of potential participants with Down syndrome will always be made through parents/guardians or organizations/service providers who work with the individuals with Down syndrome. Persons with Down syndrome will never self identify for the study. Organizations/Service providers will identify persons eligible to provide valid consent for potential participants in their system. Parents/Guardians will be presumed to have that authority if they respond on behalf of their child. Once identified, we will get signed consent from parents/guardians to ask their children to volunteer to participate in the project. Participants below the age of majority to consent for research and those who are deemed ineligible to consent for themselves due to cognitive impairment will be covered by the signature of parents/guardians. Second, all participants will only be included if they agree through assent or consent to participate. Participants below the age of 18 (the youngest age of majority we have found) will be required to provide verbal assent. Participants above the age of 18 will provide signed Assent/Consent using the document provided. Participants above the age of majority to consent to participate in research and participants deemed eligible to sign for themselves by the parents/guardian will be covered by their own consent document. For the rest, the signature will be treated as assent to participate, with the consent of the participants' parents/guardians providing the necessary informed consent documentation. All rights and considerations due to participants will be bestowed on the basis of these two signed documents. We will use the consent forms that have been approved by the IRB already. At this time, we have identified the age of majority to participate in Clinical Trials research to be 18 years for most states, with exceptions being Indiana (21), Mississippi (21), Nebraska (19), and New York (21).

5. Explain the criteria you will use for determining when assent is required for participants who are not competent.

The study procedures will be described in terms that are understandable. All individuals will be informed that it is their choice to participate. They will be given the option to say they do not want to participate. They will only be included if they respond to our request to participate in the affirmative.

6. Explain what methods will be used for evaluating dissent (e.g., description of behaviors that would indicate individual does not want to participate (such as moving away, certain facial expressions, head movements, etc...).

Participants who are slow to engage in the procedures, frown or shake their heads while participating, or appear reluctant to continue will be excused for the current session. IF they appear reluctant for two sessions in a row - they will be excused from the study.

7. The research protocol should include someone who can be reasonably assumed to have the participant's best interest in mind and can assist the participant in navigating the consent and research process. A person holding durable power of attorney or other legal designee, spouse, close relative who is involved in ongoing care of participant, other person with a personal or blood relationship who is involved in ongoing care of participant, or other close relatives or friends may assume this role. Describe how individuals will be identified to serve in this capacity. If this request is not appropriate for this study, justify why it should be waived.

Parents/legal guardians will serve this purpose.

8. If applicable, describe when and how the individual's health care provider will be consulted prior to participation in the research. NOTE: If the Principal Investigator (PI) is also the individual's health care provider, address how the PI will separate the roles of clinician and researcher.

   NA

9. Will the research interfere with current therapy or medications? N

   If yes, describe what the changes may entail (i.e., if the subjparticipantl be removed from routine drugs/treatments, wash out periods, etc.) and the potential risks.

10. Does your research involve institutionalized individuals? N

    a) Justify the use of institutionalized individuals and explain why non-institutionalized individuals can not be substituted.

Section 3.

Complete this section if your research involves individuals from the Department of Veterans Affairs (VA).

1. Address procedures you will use to ensure the participant's representative is informed regarding his/her role and obligation to protect the incompetent participant or person with impaired decision-making capacity.

   N/A

2. Address procedures you will use to ensure the participant's representative has been told of his/her obligation to try to determine what the prospective participant would do if competent, or if the prospective participant's wishes cannot be determined, what the participant's representative thinks is in the incompetent person's best interests:

   N/A

3. The VA has specific requirements and procedures for determining and documenting in the person's medical record that an individual is incompetent or decisionally-impaired. There are additional requirements if the lack of decision-making capacity is based on diagnoses of mental illness. These requirements are outlined in the Veterans Health Administration (VHA) Handbook 1200.5, Section II. Have you reviewed these requirements and included them in your procedures? N

4. Justify that the research involves no significant risks, or if the research presents probability of harm, justify that there is at least a greater probability of direct benefit to the participant:

   N/A

Note:[Veterans Health Administration Handbook 1200.5, July 15, 2003, Section 11 - Research Involving Human participants with Surrogate Consent, and Appendix D Vulnerable Populations, Section 6(c)]

Section 4.

For research involving cognitively impaired persons outside the state of Alabama, also complete this section.

a) Provide information regarding the state definition of legally authorized representative, child, decisionally-impaired, or guardian, as applicable to the research and to the federal definitions. [If the research is to be conducted in more than one state outside of Alabama, provide this information for each state.]

Note that because recruiting will extend beyond the two states, will will follow the procedures outlined below fo identify and obtain consent for participants and legally authorized representatives.

Our approach to consent to participate will include two steps. First, initial contact of potential participants with Down syndrome will always be made through parents/guardians or organizations/service providers who work with the individuals with Down syndrome. Persons with Down syndrome will never self identify for the study. Organizations/Service providers will identify persons eligible to provide valid consent for potential participants in their system. Parents/Guardians will be presumed to have that authority if they respond on behalf of their child. Once identified, we will get signed consent from parents/guardians to ask their children to volunteer to participate in the project. Participants below the age of majority to consent for research and those who are deemed ineligible to consent for themselves due to cognitive impairment will be covered by the signature of parents/guardians. Second, all participants will only be included if they agree through assent or consent to participate. Participants below the age of 18 (the youngest age of majority we have found) will be required to provide verbal assent. Participants above the age of 18 will provide signed Assent/Consent using the document provided. Participants above the age of majority to consent to participate in research and participants deemed eligible to sign for themselves by the parents/guardian will be covered by their own consent document. For the rest, the signature will be treated as assent to participate, with the consent of the participants' parents/guardians providing the necessary informed consent documentation. All rights and considerations due to participants will be bestowed on the basis of these two signed documents. We will use the consent forms that have been approved by the IRB already. At this time, we have identified the age of majority to participate in Clinical Trials research to be 18 years for most states, with exceptions being Indiana (21), Mississippi (21), Nebraska (19), and New York (21).

Definitions:

Assent - is defined as a child's or decisionally-challenged individual's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Competence "Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice." [OHRP Institutional Review Board Guidebook, Chapter VI, Section D]

Permission is defined as the agreement of parent(s) or guardian to the participation of their child or ward in research or clinical investigation. Permission includes the element of consent set forth in federal regulations and outlined in the informed consent template included in the IRB expedited and full review applications.

In Alabama child/children refers to all individuals less than 18 years of age unless the individual(s) is/are legally emancipated. (See Guidance: Alabama Law on Children, Minors, Consent, and Other Research-Related Topics. Individuals less than 18 years of age who are not emancipated meet the federal definition for "child" (e.g., Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), and U.S. Department of Education).

Legally authorized representative (LAR) is an individual who has the authority to make research participation decisions on behalf of another. Alabama law does not specify who may make such decisions. UA legal counsel recommends the following in this order of preference: A legally appointed guardian, a health care proxy or person authorized to make medical decisions in conjunction with a durable power of attorney, a spouse, an adult child, next of kin, or a person or agency acting in loco parentis.

NOTE: Consent from a legally authorized representative involves all the ethical and regulatory concerns that apply to consent from the prospective participant.

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* * * Subject Population(p) * * *

Research Involving Prisoners

NOTE: Investigators, please include this information with the e-Protocol application if your research involves prisoners. This includes studies of known prisoners and studies recruiting participants at risk of becoming involuntary prisoners, such as participants with histories of substance abuse. Remember that persons involuntarily committed to mental health facilities (Taylor Hardin Secure Mental Health Facility, Mary Starke Harper, etc.) by the courts are also prisoners.

If participants unexpectedly become prisoners, go directly to SECTION FOUR of this form.

If your research involves prisoners with more than one vulnerability (i.e., prisoners who are also children or pregnant, are involuntarily committed to mental health facilities), attach the supplementary form for that vulnerable population as well.

Regardless of the category of your research, be sure that your application makes clear why the research must be done on prisoners.

Indicate the category that best represents your research by checking the applicable box below, and explain in the space provided for that category why your research meets the criteria.

Note: For research involving prisoners, the definition of minimal risk refers to the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental or psychological examination of healthy persons.

Category 1 (45 CFR 46.306(a)(2)(i))

My research involves the study of possible causes, effects, processes of incarceration, and of criminal behavior. (Processes of incarceration can be interpreted broadly to include substance abuse research, half-way houses, counseling techniques, criminal behavior, etc.)

Justify how the research presents no more than minimal risk and no more than inconvenience to the participants:

Category 2 (45 CFR 46.306(a)(2)(ii))

My research involves the study of prisons as institutional structures, or of prisoners as incarcerated persons. (This category is usually used fairly narrowly as when looking at prisoner diet and conditions of prison life.)

Justify how the research presents no more than minimal risk and no more than inconvenience to the participants

Category 3 (45 CFR 46.306(a)(2)(iii))

My research involves the study of conditions particularly affecting prisoners as a class. (This category is less frequently used than the previous ones and refers to such research as vaccine trials, research on hepatitis, and social and psychological problems such as alcoholism, drug addiction, and sexual assaults. Minimal risk studies should not go under this category.) For DHHS-funded research, OHRP has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of its intent to approve such research.

Note: Contact the Office of Research Compliance at (205) (348-8461 for more information

Explain what condition(s) will be studied and provide rationale for each:

Category 4 (45 CFR 46.306(a)(2)(iv))

My research involves the study of practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the participant. (Note: It is rare for research involving placebo or control groups to fall in this category because of the difficulty in justifying improvement of the health or well-being of

the participant being given placebo or in a control group.) For DHHS-funded research which requires the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after OHRP has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of its intent to approve such research.

Note: Contact the Office of Research Compliance at (205) 348-8461 for more information.

Explain the research practices that will be used in this study and how they are intended to improve the health and well-being of the participants:

Section 2. [45 CFR 46.305]

Note: When an IRB is reviewing a protocol in which a prisoner will be a participant, the IRB must find and document justification that six additional conditions are met. Describe in the space provided how each condition applies to your research.

1. Advantages acquired through participation in the research, when compared to the prisoners' current situation, are not so great that they impair their ability to weigh risks.

   Describe the possible advantages that can be expected for prisoner participants:

2. Risks are the same as those that would be accepted by non-prisoners.

   Describe the possible risks that can be expected for prisoner participants and justify that they are the same as for non-prisoners:

3. Procedures for selection are fair to all prisoners and are immune from intervention by prison authorities in prisons; control participants must be randomly selected.

   a) **Describe how prisoners will be selected for participation:**

   b) **Describe what measures will be taken to prevent intervention by prison authorities in the selection process:**

4. Parole boards cannot take into consideration a prisoner's participation in research. Informed consent must state participation will not affect length of sentence or parole.

5. For studies that require follow-up, provisions are made including consideration for the length of individual sentences; informed consent must reflect provisions for follow-up.

   Describe what provisions have been made for follow-up and how this information will be relayed to the prisoner participants:

6. Information about the study is presented in a language understandable to prisoners.

   Describe what efforts have been made to present information about the study in a language that is understandable to the prisoner population. This may mean a non-English language or an appropriate reading level in whatever language the prisoner uses.:

Section 3. Only complete if applicable: Epidemiologic Research Involving Prisoners and Funded by the Department of Health and Human Services (DHHS)

Note: Effective June 20, 2003, DHHS adopted policy that allows waiver of the requirement for

documenting applicability of a 45 CFR 306(a)(2) category (as found in Section 1 of this form) for certain epidemiologic research involving prisoners. This waiver applies to DHHS conducted or supported epidemiologic research on prisoners that presents no more than minimal risk and no more than inconvenience to the prisoner-participants.

Check the box below if your research meets the listed criteria, then provide justification in the space provided.

1. My research is funded by HHS and I request a waiver for meeting the category conditions under Section 1 of this form.
2. My research involves epidemiologic research intended to describe the prevalence/incidence of a disease by identifying all cases, or to study potential risk factor associations for a disease; and
3. Prisoners are not the sole focus of my research.

Justify how the research presents no more than minimal risk and no more than inconvenience to the participants:

Section 4. Complete if applicable:

Prisoners are not the targeted population

Note: Although prisoners may not be the target population for your research, a participant could become a prisoner during the course of the study (particularly if studying a subject population at high-risk of incarceration).

Note: If you did not receive IRB approval for involvement of prisoners, and a participant becomes a prisoner during the study, all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated participant must cease until IRB approval has been issued for their continuation in the research. If you need IRB approval for a prisoner participant to continue participation in your research, select and complete the applicable category from Section 1, complete section 2 and this section, then submit for IRB review.

In special circumstances in which the Principal Investigator asserts that it is in the best interest of the participant to remain in the research study while incarcerated, the IRB Chairperson may determine that the participant may continue to participate in the research prior to satisfying the requirements of Subpart C. However, subsequent IRB review and approval of this completed form, documenting that the requirements of Subpart C are met, is required.

Prisoners are not a target population for my research, but a participant became a prisoner during the study and I am seeking IRB approval so the participant can continue participation in the research.

Explain the importance of continuing to intervene, interact, or collect identifiable private information during the participant's incarceration:

Note: Prisoner: An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statue; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism,) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution [45 CFR 46.303(c)]. Note: Persons on Probation and parole are usually NOT considered to be prisoners.

If you will receive or are seeking Department of Health and Human Services (HHS) funding for this study, a certification letter must be submitted to the Office for Human Research Protections (OHRP). The research cannot be initiated until OHRP issues approval. The Office of Research Compliance (ORC) will prepare and submit the certification report to OHRP. Contact the Director for the Office of Research Compliance at 205-348-8461 8641 for more information.

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* * * Risks * * *

8. Risks

There is no research that can be considered totally risk free (e.g., a potential risk of breach of confidentiality). Therefore, when describing the risk, the lowest level of risk is "no more than minimal risk".

a) **For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk,a statement to this effect should be included. (In describing these risks in the consent form to the participant, it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology).**

Address any risks related to (input N/A if not applicable):

1. Use of investigational drugs. Please include the clinical adverse events (AEs) associated with each of the drugs with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure. NOTE: Include any likely adverse effects associated with placebos or washout periods that participants may experience while in the study.

   N/A

2. Use of investigational devices. Please include the clinical adverse events (AEs) associated with each of the devices with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure. NOTE: Include any likely adverse effects associated with procedures that participants may experience while in the study.

   N/a

3. Use of FDA approved drugs, reagents, chemicals, or biologic products. Please include the clinical adverse events (AEs) associated with each of the drugs with an indication of frequency, severity and reversibility. This information can often be found in the package insert provided by the manufacturer. NOTE: Include any likely adverse effects associated with placebos or washout periods that participants may experience while in the study.

   N/A

4. Use of FDA approved devices. Please include the clinical adverse events (AEs) associated with each of the devices with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure. NOTE: Include any likely adverse effects associated with procedures that participants may experience while in the study.

   N/A

5. Describe any risks related to performing study procedures. Please include all investigational, non-investigational, and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

   N/A

6. Describe any risks related to the use of radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy).

   N/A

7. For clinical studies (of a drug, vaccine, device or treatment), describe any alternative procedure(s) or course(s) of treatment. List important risks and benefits of these alternatives in order to compare to study procedure(s) or course(s) of treatment. This information MUST be included here. Any standard treatment that is being withheld must be disclosed and the information must be included in the consent form.

   N/A

8a. Describe any other physical, psychological, social or legal risks the participant may experience.

Mild boredom/fatigue is possible but unlikely. Sessions are relatively short and involve game-like activities.

8b. Data Safety Monitoring

Is there a Data Monitoring Committee (DMC) or Board (DSMB)? N

If yes, describe its role, if it is independent of the sponsor or research team, the make-up of the Board and their qualifications, and how often the Board will meet.

If no, please justify why not.

The nature of the data do not require a DMC.

Is there a Data Safety Monitoring Plan (DSMP)? Y

If yes, describe the data and safety monitoring plan developed to ensure the safety of participants and the validity and integrity of research data. Monitoring should be commensurate with risks and with the size and complexity of the trials. As such, state that SAEs will be reviewed by a qualified MD in real time and indicate how often aggregate data will be reviewed for safety trends.

Rationale. The Data Safety and Monitoring Plan (DSMP) for our intervention research on Assessing the Malleability of Spatial Abilities in Downs Syndrome has two specific goals (1) to ensure the confidentiality of all data, and (2) to ensure that participant experiences are positive by minimizing fatigue and frustration.
Design of DSMP. Prior to the initiation of testing, Drs. Merrill and Yang will train Graduate and Undergraduate assistants on monitoring participants for expressions of fatigue and frustration. They will be providing strategies for alleviating any difficulties that may arise. On-going monitoring of potential problems will take place during our bi-weekly meetings, with Montclair State and University of Alabama communicating via Skype or Facetime. We will discuss the number of participants tested over the two week period, ensure that identifying information is not stored with any data, and that data has been recorded without identifiers in UA Box (a secure cloud storage service for UA faculty). Data will be shared between sites via UA Box, to which both PIs have access (Dr. Yang is a former Graduate student and still has UA Access). All information that can be used to identify participants will be locked in the offices of Dr. Merrill and Dr. Yang. We will also evaluate whether or not participants have exhibited any fatigue and frustration during the testing period and review how that was resolved. If necessary, additional procedures to ensure that participants get adequate breaks and refreshments during each session will be implemented. Any additional and unforeseen adverse events will be discussed and plans will be implemented to prevent future difficulties.
Reporting of Adverse Events. Research personnel will be told to report all suspected adverse events immediately to Dr. Yang and Dr. Merrill. Dr. Merrill will report these events to the research team and the appropriate IRB personnel. All adverse events will be discussed at the next bi-weekly meeting of the research team. The PIs will amend the research protocol if a serious adverse event occurs that is found to be the result of the protocol.

If no, please justify why not.

*** * * Benefits/Alternatives, Procedures to Maintain Confidentiality * * ***

9. Benefits/Alternatives

a) **Benefits. Describe the potential benefit(s) to be gained by the participants and how the results of the study may benefit future participants and/or society in general. Indicate if there is no direct benefit to the**

may benefit future participants and/or society in general. Indicate if there is no direct benefit to the participants.

Participants may benefit from improved spatial abilities that can positively impact performance in everyday activities.

b) **Alternatives. Describe any alternative treatments and procedures available to the participants should they choose not to participate in the study. If no such alternatives exist, please state that the alternative is nonparticipation. For some studies, such as record reviews, a description of alternatives would not be applicable.**

The alternative is nonparticipation.

10. Procedures to Maintain Confidentiality

Federal regulations require that study data and consent documents be kept for a minimum of three (3) years, and HIPAA documents be kept for a minimum of six (6) years after the completion of the study by the PI. For longitudinal or sponsored projects, the PI may be required to keep the data and documents for a longer time period.

Data Security

Please indicate how information will be secured. All information must be stored using at least two of the following safeguards and must be kept in accordance with the University of Alabama Information Security Policies. (If you are using both electronic data and hard copy data, you will need two safeguards for each type).

a) Electronic Data: (mark all that apply - at least 2 - or indicate not applicable)

- [ ] Not applicable
- [X] Password access
- [X] Coded, with a master list kept as a hardcopy or on a secure network (confidential)
- [ ] Data collected anonymously
- [ ] Secure network (e.g., firewall)
- [X] Data are de-identified by PI or research team
- [ ] Other

Please specify:

b) Hardcopy Data: (mark all that apply - at least 2 - or indicate not applicable))

- [ ] Not applicable
- [ ] Locked suite
- [X] Locked office
- [ ] Locked file cabinet
- [X] Coded, with a master list secured and kept separately (confidential)
- [ ] Data collected anonymously
- [ ] 24 hour personnel supervision
- [ ] Data are de-identified by PI or research team
- [ ] Other

Please specify:

c) Describe measures employed to protect the identity of the participants, their responses, and any data that you obtain from private records (e.g., identifiers will be stripped so data cannot be linked to participants, or code numbers will be used, etc.). If data will be coded, specify the procedures for coding the data so that confidentiality of individual participants is protected. If you will keep a master list linking study codes to participant identifiers, explain why this is necessary, how and where you will secure the master list, and how

long it will be kept.

All data will be identified by number rather than name. The PI at each site will keep a master list of names and number codes that will be in a locked office until data collection is complete for each participant. After that time, all identifiers will be removed and it will be impossible to link the data to any specific participant. Data will be shared between sites via UA Box, to which both PIs have access (Dr. Yang is a former Graduate student and still has UA Access).

d) If data or specimens are being shared outside of the research team, indicate who will receive the material and specifically what they will receive (data or specimens).

N/A

e) If samples or data will be provided from an outside source, indicate whether you will have access to identifiers, and, if so, how identifiable information is protected. Please provide a letter from the appropriate persons indicating that data will be provided in a de-identified manner.

N/A

f) If data will be collected via e-mail or the internet, how will anonymity or confidentiality be protected? Describe how data will be protected during electronic transmission and how data will be recorded (i.e., will internet protocol (IP) address and/or e-mail addresses be removed from data?).

g) If you will be audio/video recording or photographing participants, provide a rationale for recording/photographing. Describe confidentiality procedures, including the final disposition of the recordings/photos (destruction, archiving, etc.) and a reasonable timeline by which this disposition will occur.

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* * * Potential Conflict of Interest * * *

11) Potential Conflict of Interest

Federal regulations and UA policy require all investigators to disclose their significant financial interests to allow a review of potential conflicts of interest. If a potential conflict of interest is identified, a formal plan must be developed and implemented to manage, reduce, or eliminate the conflict.

Examples of significant financial interests include receipt of income, honoraria, and stock or stock options from a public or private entity sponsoring the research. They may also include a consulting arrangement or membership on an advisory board of the entity. Significant financial interests are reported on the UA Statement of Financial Interest.

All members of the research team who are involved in the design, conduct, or reporting of research (i.e., senior/key personnel) should have a current Statement of Financial Interest and conflict of interest training on file prior to submitting the IRB protocol. Please refer to the Office for Research Compliance website for additional information regarding the financial conflict of interest requirements, as well as links to the disclosure form and training at (http://osp.ua.edu/site/RC_CoI.html).

The Statement of Financial Interest must be submitted annually and within 30 days of discovering or acquiring a new or increased financial interest. Conflict of interest training must be completed once every four years.

If such a relationship as described above exists between a member of the research team and the sponsor of the research, the investigator is also required to disclose this relationship and identify the entity involved on the informed consent form.

For questions regarding Conflict of Interest consult the Conflict of Interest in Research

Policy.

Check one of the following:

1) X No Financial Interest or Financial interest less than or equal to $5K
2) Financial Interest exceeding $5K but not exceeding $25K, and/or more than 5 percent equity interest in aggregate
3) Financial Interest exceeding $25K

Check all those that apply:

Consulting

Speaking Fees or Honoraria

Gifts

Patent

Copyright

Licensing agreement or royalty income

Equity interests, (including stock, stock options, warrants, partnership or equitable ownership interests), or serving on a scientific advisory board or board of directors

Other fees/compensation

Describe financial interests(s) and indicate specific amounts for each subcategory checked. Be sure to describe how these financial interests relate to the protocol being submitted.

Note to Investigator(s) Reporting a Potential Conflict of Interest

Investigator(s) must have:

1) Current, up-to-date Conflict of Interest Disclosure Form on file with the University of Alabama Conflict of Interest Committee (COIC) that describes any financial relationship indicated above.

. This information must be disclosed on the University of Alabama confidential Conflict of Interest Disclosure Form for review by the COIC before accruing research participants in this study. If your current Disclosure Form does not contain this information, you are required to submit an updated Disclosure Form to the COIC.

2) Financial disclosure statement incorporated into the consent document. Please see Model Consent for suggested language.

3) You may not begin your study until your disclosure form has been reviewed and any required management plan has been approved by the COIC.

Does any member of the study team, members' spouses, or members' dependent children have any significant financial interests related to the work to be conducted as part of the above-referenced project? N

Name of Personnel with Financial Conflict of Interest

Other research staff that may have a conflict. Please specify below.

Any member of the study team who answers in the affirmative must be listed in the box below.

A staff person will contact any researcher listed above to obtain additional information regarding the specific financial interest(s).

I certify that all members of the study team have answered the financial interests question and only those individuals listed in the box above have disclosed any financial interest related to this study. Y

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* * * Informed Consent * * *

12 Informed Consent

Federal regulations require that informed consent be obtained from individuals prior to their participation in research unless the IRB grants a waiver of consent. Answer the questions, below, then click Add to provide the necessary consent documents and information regarding participant consent. Multiple consents/waivers may be added, but they must be uploaded one at a time.

NOTE: You may refer to the University of Alabama IRB Guidance for Obtaining Informed Consent for considerations regarding the consent/assent process.

State N/A if not applicable.

1) **How is consent being obtained? When and where will the discussion take place?**

Parents/guardians will be sent consent forms and asked to return them to the PI at the appropriate location. Adults participants will be consented at the start of the study. All adult participants with Down syndrome will be read the consent aloud.

2) **Explain how risks, benefits, and alternatives will be discussed.**

They will be read on the consent. The consent will be read aloud to participants with down syndrome. Questions will be answered if any arise.

Informed Consent

Title	Consent Type	Attached Date
Remote Testing - Adult Participant Consent	Consent	11/14/2020
Parent Consent to Record	Consent	11/14/2020
Adult Participant Consent to Record	Consent	02/09/2021
Consent for Scheduling Flexibility	Addendum Consent	05/15/2021
Remote Testing - Parent Consent - New Control	Consent	08/09/2022

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* * * Assent * * *

13 Assent

Complete this section if your study includes minors. An assent document should be used if participants are 6 to 18 years of age. The Assent Form Template provides guidelines for writing assent documents.

1) **Will minors be asked to give assent? If not, please justify.**

Yes

Note: For studies that require a discussion about reproductive risks, note that the conversation with the minor should take place separately from the parents. Also, if a minor will reach adulthood (18 in Missouri) during the course of the study, they will need to be asked to consent as an adult at that time to continue in the study.

Assent Documents

Title	Upload assent document	Attached Date
Basic Assent Script	Basic Script for Assent 10.10.2019	10/10/2019
Assent to Record Sessions	Assent to Record Child Participant	02/09/2021

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* * * HIPAA * * *

14 HIPAA

Studies that receive or create protected health information (PHI) are subject to HIPAA regulations. PHI is health information with one or more personal identifiers. For more information see: http://www.ua.edu/research/index.html

If you are working with UMC, then a separate IRB approval is required. This must be obtained prior to IRB submission and attached.

1) **Will health information be accessed, received or collected?**

X No health information. HIPAA does not apply.

Yes (continue to question 2).

2) **Which personal identifiers will be accessed, received or collected?**

No identifiers. I certify that no identifiers from the list below will be received or collected and linked to health information. HIPAA does not apply (skip remainder of page).

Names

Social Security numbers

Telephone numbers

Linkable code or any other unique identifying number (note this does not mean the unique code assigned by the Investigator(s) to code the research data)

All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000

All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

Fax numbers

Electronic mail addresses

Medical record numbers

Health plan beneficiary numbers

Account numbers

Certificate/license numbers

Vehicle identifiers and serial numbers, including license plate numbers

Device identifiers and serial numbers

Web Universal Resource Locations (URLs)

Internet Protocol (IP) address numbers

Biometric identifiers, including finger and voice prints

Full face photographic images and any comparable images

If you are receiving or collecting health information and at least one personal identifier, HIPAA applies to your study. Please continue to complete the sections, below.

3) **Sources of Protected Health Information:**

Hospital/medical records for in or out patients

Physician/clinic records

Laboratory, pathology and/or radiology results

Biological samples

Interviews or questionnaires/health histories

Mental health records

Data previously collected for research purposes

Billing records

Other

Please describe:

4) **If data will be shared outside the research team and the study involves PHI indicate how the research team will share the information. Contact the University of Alabama Privacy Officer for guidance on the proper procedures for sharing of protected health information. http://hipaa.ua.edu/**

Not applicable (continue to question 5).

Only linkable code that can link data to the identity of the participant. A code access agreement or business associate agreement may be needed when data are shared with other non-University of Alabama entities. If necessary, the agreement can be added and uploaded in item #5, below.

Limited identifiers: Zip codes, dates of birth, or other dates only. The study qualifies as a Limited Data Set. A data use agreement may be needed when data are shared with other non-AlaUniversity of Alabamatities. If necessary, the agreement can be added and uploaded in item #5, below.

With unlimited identifiers. The consent document and HIPAA Authorization form must describe how the information will be disclosed.

5) **A HIPAA Authorization Form or Waiver of HIPAA Authorization is required for this study. Use the table below to add HIPAA Documents for your study. If you are accessing medical records, or other health records that include PHI, you must complete a waiver of HIPAA authorization.**

*** * * Attachments * * ***

15) Attachments

In this section, please upload additional documents associated with your protocol. Failure to attach files associated with the protocol may result in the protocol being returned to you.

Possible documents for this protocol could include:

Bibliography

Cooperating Institution's IRB Approval

Data Collection Sheet

Debriefing Script

Device Information/Documentation

Grant Proposal/Sub-Contract

Human Participants Training Certificate/Proof of Training

IND Application Letter

Information Sheet/Brochure

Interview/Focus Group Questions

Investigator's Brochure

Letter of Agreement/Cooperation

Package Insert
Patient Diary Form
Phone Script
Questionnaire/Survey
Recruitment Material (e.g., flyers, ads, e-mail text)
Recruitment Statement (if there is no waiver of written consent)
Scientific/PPC Review
Sponsor's Protocol
Sponsor's Protocol Amendment
Study Design Chart/Table
Waiver Request
Other files associated with the protocol (most standard formats accepted: pdf, jpg, tif, mp3, wmv, etc.)

To update or revise any attachments, please delete the existing attachment and upload the revised document to replace it.

Document Type	Document Name	Attached Date	Submitted Date
Grant Proposal/Sub-Contract	Assessing Malleability	08/15/2019	08/15/2019
Other	Ltr UofA IAA Yang	09/10/2019	09/10/2019
Other	Merrill app w rev	09/27/2019	09/27/2019
Other	IRB Cover Letter - Response to Full Board Review	10/07/2019	10/07/2019
Other	Merrill 19-016	10/23/2019	10/23/2019
Other	Addendum Cover Letter	07/23/2020	07/23/2020
Cooperating Institution's IRB Approval	Merrill IRB Authorization Agreement MSU UofA	07/23/2020	07/23/2020
Other	Merrill 19-016 A	07/27/2020	07/27/2020
Other	Merrill fully executed agreement	07/27/2020	07/27/2020
Other	Merrill app w rev Sept 2020	09/22/2020	09/22/2020
Other	Merrill 19-016-R1 (eP 19-08-2644)	10/30/2020	10/30/2020
Other	Addendum 2 Cover Letter	11/14/2020	11/14/2020
Recruitment Material (e.g., flyers, ads, e-mail text)	Contact Letter for Parents Identified by Schools or Service Providers Malleability	11/14/2020	11/14/2020
Other	Merrill app w rev Dec 2020	12/18/2020	12/18/2020

Other	Merrill Dec 2020 app w rev	12/18/2020	12/18/2020
Other	Merrill 19-016-R1 A FB approval	03/04/2021	03/04/2021
Other	Merrill 19-016-R1 B	04/12/2021	04/12/2021
Recruitment Material (e.g., flyers, ads, e-mail text)	Merrill Research Page	05/15/2021	05/15/2021
Letter of Agreement/Cooperation	Michelle Darabaris Approval	05/15/2021	05/15/2021
Recruitment Material (e.g., flyers, ads, e-mail text)	Strategic Communications	06/08/2021	06/08/2021
Other	Merrill 19-016-R1 C	06/21/2021	06/21/2021
Other	Merrill approval 19-016-R2	09/17/2021	09/17/2021
Other	Merrill 19-016-R3	08/22/2022	08/22/2022
Recruitment Material (e.g., flyers, ads, e-mail text)	UnStamped DS Kids Flyer Lab	07/14/2023	07/14/2023
Recruitment Material (e.g., flyers, ads, e-mail text)	UnStamped Typical Kids Flyer Lab	07/14/2023	07/14/2023
IRB Approval	Merrill 19-016-R4_19-08-2644_Approval	08/21/2023	08/21/2023
IRB Approval	Merrill 19-016-R4-A Approval	09/27/2023	07/15/2024
Human Subjects Training Certificate/Proof of Training	citiCompletionCertificate_Jennifer Yang	08/07/2024	08/07/2024
Human Subjects Training Certificate/Proof of Training	Stephanie Grinshpun CITI	08/07/2024	08/07/2024
Human Subjects Training Certificate/Proof of Training	citiCompletionCertificate_Zakrzewski	08/07/2024	08/07/2024
Human Subjects Training Certificate/Proof of Training	CITI Program Completion Certificate 61800939	08/07/2024	08/07/2024
IRB Approval	Merrill_19-016-R5_19-08-2644_Approval	08/08/2024	

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* * * PI Obligations * * *

PI Obligations

By clicking the box below, you indicate that you accept responsibility for and will follow the ethical guidelines.

1) Have you completed the annual Statement of Financial Interest (i.e., disclosure)? Y

NOTE: An annual disclosure must be completed by all faculty, staff, and students who are identified as senior/key personnel receiving federal funding for research. The disclosure can be completed online at https://www.formstack.com/forms/index.php?1338617-e6Kw9EILFS.

2) Have your financial interests changed significantly since you completed the annual disclosure form? N

According to the UA policy on conflict of interest, it is the PI's responsibility to inform co-investigators, staff, or students involved in the design, conduct, or reporting of federally sponsored research of their requirement to complete the Statement of Financial Interest.

X **I accept this responsibility.**

By submitting this form, the PRINCIPAL INVESTIGATOR certifies that he/she has read the UA policy on conflict of interest and has a current Statement of Financial Interest on file. In addition, the PI certifies that, to the best of his/her knowledge, no person working on this project at UA has a conflict of interest or, if a conflict of interest does exist, an appropriate management plan is in place.

X **The Principal Investigator has read and agrees to abide by the above obligations.**

The Department Chair has read and agrees to abide by the above obligations.

The Faculty Sponsor / Mentor has read and agrees to abide by the above obligations.

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* * * Event History * * *

Event History

Date	Status	View Attachments	Letters
08/08/2024	CONTINUING REVIEW 5 FORM APPROVED	Y	Y
08/08/2024	CONTINUING REVIEW 5 FORM REVIEWER(S) ASSIGNED		
08/07/2024	CONTINUING REVIEW 5 FORM RESUBMITTED	Y	
07/22/2024	CONTINUING REVIEW 5 FORM RETURNED		
07/15/2024	CONTINUING REVIEW 5 FORM SUBMITTED	Y	
07/15/2024	CONTINUING REVIEW 5 FORM CREATED		
09/27/2023	AMENDMENT 6 FORM APPROVED	Y	Y

09/27/2023	AMENDMENT 6 FORM REVIEWER(S) ASSIGNED		
09/27/2023	AMENDMENT 6 FORM PANEL REASSIGNED		
09/15/2023	AMENDMENT 6 FORM SUBMITTED	Y	
09/15/2023	AMENDMENT 6 FORM CREATED		
08/21/2023	CONTINUING REVIEW 4 FORM APPROVED	Y	Y
08/10/2023	CONTINUING REVIEW 4 FORM REVIEWER(S) ASSIGNED		
07/14/2023	CONTINUING REVIEW 4 FORM SUBMITTED	Y	
07/12/2023	CONTINUING REVIEW 4 FORM CREATED		
08/22/2022	CONTINUING REVIEW 3 FORM APPROVED	Y	Y
08/11/2022	CONTINUING REVIEW 3 FORM REVIEWER(S) ASSIGNED		
08/10/2022	CONTINUING REVIEW 3 FORM SUBMITTED	Y	
08/09/2022	CONTINUING REVIEW 3 FORM CREATED		
08/09/2022	AMENDMENT 5 FORM DELETED		
08/09/2022	REPORT 2 FORM CREATED		
07/14/2022	AMENDMENT 5 FORM RETURNED		
07/14/2022	AMENDMENT 5 FORM SUBMITTED	Y	
07/14/2022	AMENDMENT 5 FORM CREATED		
09/17/2021	CONTINUING REVIEW 2 FORM APPROVED	Y	Y

09/09/2021	CONTINUING REVIEW 2 FORM REVIEWER(S) ASSIGNED		
08/11/2021	CONTINUING REVIEW 2 FORM SUBMITTED	Y	
08/11/2021	CONTINUING REVIEW 2 FORM CREATED		
06/21/2021	AMENDMENT 4 FORM APPROVED	Y	Y
06/17/2021	AMENDMENT 4 FORM REVIEWER(S) ASSIGNED		
06/10/2021	AMENDMENT 4 FORM REVIEWER(S) ASSIGNED		
06/08/2021	AMENDMENT 4 FORM RESUBMITTED	Y	
06/02/2021	AMENDMENT 4 FORM RETURNED		
05/15/2021	AMENDMENT 4 FORM SUBMITTED	Y	
05/15/2021	AMENDMENT 4 FORM CREATED		
04/12/2021	AMENDMENT 3 FORM APPROVED	Y	Y
04/08/2021	AMENDMENT 3 FORM REVIEWER(S) ASSIGNED		
04/08/2021	AMENDMENT 3 FORM RESUBMITTED	Y	
04/07/2021	AMENDMENT 3 FORM RETURNED		
03/22/2021	AMENDMENT 3 FORM SUBMITTED	Y	
03/22/2021	AMENDMENT 3 FORM CREATED		
03/04/2021	AMENDMENT 2 FORM APPROVED	Y	Y
03/04/2021	REPORT 1 FORM CREATED		

12/18/2020	AMENDMENT 2 FORM REVIEWER(S) ASSIGNED		
12/10/2020	AMENDMENT 2 FORM REVIEWER(S) ASSIGNED		
12/02/2020	AMENDMENT 2 FORM PANEL MANAGER REVIEW		
11/14/2020	AMENDMENT 2 FORM SUBMITTED	Y	
11/14/2020	AMENDMENT 2 FORM CREATED		
10/30/2020	CONTINUING REVIEW 1 FORM APPROVED	Y	Y
09/22/2020	CONTINUING REVIEW 1 FORM REVIEWER(S) ASSIGNED		
09/10/2020	CONTINUING REVIEW 1 FORM REVIEWER(S) ASSIGNED		
09/02/2020	CONTINUING REVIEW 1 FORM PANEL MANAGER REVIEW		
08/15/2020	CONTINUING REVIEW 1 FORM SUBMITTED	Y	
08/15/2020	CONTINUING REVIEW 1 FORM CREATED		
07/27/2020	AMENDMENT 1 FORM APPROVED	Y	Y
07/23/2020	AMENDMENT 1 FORM REVIEWER(S) ASSIGNED		
07/23/2020	AMENDMENT 1 FORM SUBMITTED	Y	
07/23/2020	AMENDMENT 1 FORM CREATED		
10/23/2019	NEW FORM APPROVED	Y	Y
10/07/2019	NEW FORM REVIEWER(S) ASSIGNED		

09/27/2019	NEW FORM REVIEWER(S) ASSIGNED	
09/13/2019	NEW FORM REVIEWER(S) ASSIGNED	
09/12/2019	NEW FORM REVIEWER(S) ASSIGNED	
09/12/2019	NEW FORM PANEL ASSIGNED	
09/10/2019	NEW FORM RESUBMITTED	Y
08/20/2019	NEW FORM RETURNED	
08/15/2019	NEW FORM SUBMITTED	Y
08/14/2019	NEW FORM CREATED	