Intervention-Induced Plasticity of Flexibility and Learning Mechanisms in ASD-IDDRC

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**List of Abbreviations**

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| AAHARP | Association for the Accreditation of Human Research Protection Program |
| ABAS | Adaptive Behavior Assessment System |
| ADHD | Attention Deficit Hyperactivity Disorder |
| ADOS | Autism Diagnostic Observation Schedule |
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| ASD | Autism spectrum disorder |
| BERD | Biostatistics, Epidemiology and Research Design |
| BRIEF | Behavior Rating Inventory of Executive Functioning |
| CDC | Center for Disease Control |
| CFMI | Center for Functional and Molecular Imaging |
| CITI | Collaborative Institutional Training Initiative |
| CNH | Children's National Hospital |
| CNS | Central nervous system |
| COI | Conflicts of Interest |
| CRF | Case report form |
| CRI | Children's Research Institute |
| CTC | Circulating Tumor Cells |
| CTSI | The Clinical and Translational Science Institute |
| DC | District of Columbia |
| DC-IDDRC | District of Columbia Intellectual and Developmental Disabilities Research Center |
| DD | Developmental disorders |
| DMN | Default mode network |
| DOB | Date of birth |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders |
| EF | Executive Function(s) |
| EFCT | Executive Function Challenge Task |
| FC | Functional Connectivity |
| FDA | Food and Drug Administration |
| fMRI | Functional Magnetic Resonance Imaging |
| GAC | Global Executive Composite |
| GCP | Good Clinical Practice |
| GRAPPA | Generalized autocalibrating partially parallel acquisitions |
| GU | Georgetown University |
| GWU | George Washington University |
| HHS | Health and Human Services |
| HIPAA | Health Insurance Portability and Accountability Act |
| ID | Intellectual Disability |
| IEP | Individualized Education Plan |
| IQ | Intelligence Quotient |
| IRB | Institutional Review Board |
| LAR | Legally Authorized Representative |
| M-fMRI | Model based functional magnetic resonance imaging |
| MB | Multiband |
| mPFC | Medial Prefrontal Cortex |
| MPRAGE | Magnetization Prepared Rapid Acquisition Gradient Echo |
| MR | Magnetic Resonance |

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| MRI | Magnetic Resonance Imaging |
| MTL | Medial temporal lobe |
| NIH | National Institute of Health |
| OHRP | The Office for Human Research Protections |
| OPHS | Office for the Protection of Human Subjects |
| PCC | Posterior cingulate cortex |
| PD | Project Director(s) |
| PET | Positron Emission Tomography |
| PHI | Personal Health Information |
| PO | Program Official |
| PPE | Personal Protective Equipment |
| RA | Research Assistant |
| RCT | Randomized Control Trial |
| REDcap | Research Electronic Data Capture |
| rsFC | Resting state functional connectivity |
| SAE | Serious Adverse Events |
| SAP | Statistical and analytical plan |
| SCQ | Social Communication Questionnaire |
| SD | Standard deviation |
| SRS-2 | Social Responsiveness Scale |
| T1 | Timepoint 1 |
| T2 | Timepoint 2 |
| T3 | Timepoint 3 |
| T4 | Timepoint 4 |
| TAU | Treatment as Usual |
| TD | Typically developing |
| TR | Repetition Time |
| UOT | Unstuck and On Target |
| UOT-ES | Unstuck and On Target - Elementary School |
| UOT-HS | Unstuck and On Target – High School |
| UP | Unanticipated problem |
| vmPFC | Ventromedial Prefrontal Cortex |
| WASI-2 | Weschler Abbreviated Scale of Intelligence, Second Edition |

**Protocol Summary**

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| **Title:** | Intervention-Induced Plasticity of Flexibility and Learning Mechanisms in ASD |
| **Brief Summary:** | Teens with autism spectrum disorder (ASD) do not readily transfer learned knowledge to novel settings. One reason for this could be their cognitive and behavioral inflexibility, which is reflected in preferences for sameness, rigidity, and adherence to familiar routines. The proposed project uses our well-established cognitive-behavioral intervention for promoting flexible behavior and neuroimaging methods to assess whether individual variability in learning mechanisms is associated with behavioral flexibility and generalization of treatment outcomes to new settings. Findings from the study will inform the development of personalized behavioral treatments for promoting adaptive behavior in youth with ASD. |
| **Study Population:** | Teens 14-18 years old with autism spectrum disorder |
| **Study Site(s):** | Center for Autism Spectrum Disorders, MC-ROC, Children's National Hospital, Georgetown University |
| **Number of Participants:** | 54 |
| **Accrual Ceiling:** | 75 |
| **Study Duration:** | 6 years |
| **Subject Duration:** | Participants will be enrolled for approximately 36 months |
| **Objective(s):** | Our primary objective is to elucidate the association between learning and flexibility by testing whether intervening to promote flexible behavior in ASD changes learning and associated neural mechanisms. |
| **Methodology:** | We employ a longitudinal case-controlled design in 54 14-18 year old youth with ASD at 3 time-points approximately 8 months apart, each including m-fMRI during category learning and behavioral measurement of executive and adaptive function in order to probe whether individual variation in learning biases (prototype/exemplar) and their neural correlates predicts behavioral flexibility at baseline (Time1) and is stable over time (Time 2). We introduce a cognitive-behavioral intervention for flexibility (Unstuck-and-On-Target-High School) that targets development of prototypical knowledge (9) after Time 2 in order to evaluate whether Intervention will strengthen prototype learning, and associated ventromedial-prefrontal cortex (vmPFC) involvement will be associated with better behavioral response to intervention. We will also probe the impact of intervention-induced plasticity of intrinsic functional connectivity in the brain. |
| **Outcome Measures:** | Adaptive Behavior Assessment System, BRIEF, EFCT, and other cognitive assessments |
| **Study Intervention/Procedures:** | Participants will complete a cognitive-behavioral intervention aimed at promoting executive functioning skills. Participants will complete 3 timepoints of assessments (T1-T3) spaced 8 months apart. These include cognitive assessments, questionnaires, parent-report questionnaires, and MRI scanning. Additionally, participants will be asked to complete follow-up online questionnaires (T4). Following an initial waitlist period of 8 months and after the second wave of assessment, all participants will receive a clinic-based group therapy program consisting of 25 weekly sessions over the span of 8 months. |

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| **Statistical Analysis:** | In this self-controlled study, and for each outcome, our primary analyses will use an analysis of variance (ANOVA) comparing the scores (EFCT Flexibility, BRIEF Shift, ABAS GAC) at all three time points. Reliability of UOT-induced change in learning bias will be assessed by using model fit values at T1 and T2 to generate test-retest distribution of mean and standard deviation (SD) (T2-T1) from the 54 participants. We will then calculate the reliable change index for T3 by deriving the Z score for each subject.<br><br>**Aims 1,2,3**<br>In this self-controlled study, and for each outcome, our primary analyses will use an analysis of variance (ANOVA) comparing the scores (EFCT Flexibility, BRIEF Shift, ABAS GAC) at all three time points. The main contrast of interest will be to compare the scores before (T2) to those after (T3) the intervention covarying for T2 pre-intervention values. In addition, we are interested in the difference of difference contrast (T3-T2) – (T2-T1) to evaluate whether the change observed pre to post intervention is higher than change during the baseline period.<br><br>Reliability of UOT-induced change in learning bias will be assessed by using model fit values at T1 and T2 to generate test-retest distribution of mean and standard deviation (SD) (T2-T1) from the 54 participants. We will then calculate the reliable change index for T3 by deriving the Z score for each subject: subject (T3-T2) minus sample mean (T2-T1) divided by sample SD (T2-T1). Responders will be categorized as Z>1.5. We also expect individual variation in prototype model fit change (T3-T2) to correlate with UOT behavioral response (T3-T2) on EFCT Flexibility, BRIEF Shift, and ABAS Composite scores such that those with a stronger prototype fits post-UOT will have more improvement in flexibility and adaptive function.<br><br>H2: We expect that vmPFC activation from the prototype regressor will be higher in responders relative to non-responders<br>(t-test). We expect T3-T2 vmPFC activation difference to correlate positively with improvement in flexibility and adaptive function<br><br>H1: vmPFC-MTL FC values and mean FC of the MTL network will correlate positively with learning model fit difference (stronger prototype learning) at T1 and T2. H2: We will test mediation of the association between T3-T2 prototype learning change and flexibility (EFCT Flexibility, BRIEF Shift) and adaptive (ABAS GAC) change (direct effect) by FC with a regression model; adding the FC values will reduce the significance of the direct effect, thus, showing that connectivity is a partial mediator. We expect the MTL network FC to be a stronger mediator than vmPFC-MTL, suggesting that UOT modulates a large-scale network dedicated to memory integration. |

## Section 1: Key Roles

- **Lauren Kenworthy (Project Director):** Dr. Kenworthy will take primary responsibility for overall coordination and implementation of all aspects of the study at Children's National. Specifically, in accordance with the multiple PD plan, Dr. Kenworthy will frequently communicate and collaborate with Dr. Vaidya, co-lead weekly research meetings, ensure the study timeline is being followed, and contribute to data analysis and interpretation. Dr. Kenworthy will also co-lead the intervention groups, along with Dr. Pugliese and Dr. Verbalis.

- **Chandan Vaidya (Project Director):** Dr. Vaidya will take primary responsibility for overall coordination and implementation of all aspects of the study at Georgetown University. Specifically, in accordance with the multiple PD plan, Dr. Vaidya will frequently communicate and collaborate with Dr. Kenworthy, co-lead weekly research meetings, ensure the study timeline is being followed, and contribute to data analysis and interpretation. Dr. Vaidya will be responsible for overseeing all neuroimaging procedures and data analysis.
- **Xiaozhen You (Co-Investigator):** Dr. You is Research Faculty within the Children's Research Institute (CRI) of CNH and Research Assistant Professor at GWU-School of Medicine. Dr. You is an expert in neuroimaging analysis including developing novel methods for whole-brain functional connectivity analysis and applying them to developmental clinical populations. Dr. You's duties on the proposed project will include implementing the neuroimaging data processing pipeline that will contain quality assurance checks as well as individual analysis, supervising preprocessing and conducting the proposed group and dimensional analyses.
- **Cara Pugliese (Co-Investigator):** Dr. Pugliese will support Dr. Kenworthy in the coordination and implementation of this project at Children's National. She will assist with training and overseeing the research staff in administering characterization and study measures, and will be the lead interventionist, supervising the other members of the intervention team, as well as participating in conformation of diagnosis and collection of study measures across all aims of the project.
- **Alyssa Verbalis (Project Lead):** Dr. Verbalis will supervise the research assistants on developing the IRB protocol and assist with IRB coordination across sites. She will support the training of the research assistant and postdoc on behavioral assessment measure, as well as coordinate data collection. She will co-lead intervention groups, along with Drs. Pugliese and Kenworthy. She will assist Dr. Kenworthy with all aspects of the project.
- **CNH Postdoctoral Fellow***:* The CNH fellow included in this project will be trained and become research reliable on the administration of the ADOS. They will assist with confirming diagnoses as well as administering additional characterization and study measures across all aims of the project. The fellow will also assist with co-leading intervention groups.
- **GU Postdoctoral Fellow:** The GU fellow included in this project will have extensive experience with neuroimaging. They will assist Dr. You and Vaidya in all neuroimaging data analysis.
- **CNH and GU Research Assistants (RA):** The RAs for this project will work under the direction of the Project Directors and Project Lead to assist with recruitment, IRB management, scheduling assessments and trainings, ordering supplies and intervention materials, conducting assessments, collecting data, daily management of study data, and scoring and data entry of assessments. The RAs may also be involved in intervention groups to support the primary interventionist.

| **Principal Investigators** | |
|---|---|
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## Section 2: Introduction, Background Information and Scientific Rationale

### 2.1 Background Information and Relevant Literature

**The Challenge: Problems with flexibility impede generalization of learning in ASD**

**Learned skills and knowledge do not consistently generalize to new contexts despite strong rote memory and intelligence in ASD (1, 20-23). This enduring challenge limits the effectiveness of treatments (13), leads to poor outcomes (11, 12), and prevents many autistic people from sharing their talents and expertise with society.** Successful generalization of skills during adolescence and

adulthood requires the ability to spontaneously apply prior knowledge to novel situations without explicit direction or structure. Despite evidence that young autistic teens can demonstrate *proximal* generalization (i.e. an isolated trained skill is demonstrated with a new person in a structured setting (24)), *distal* generalization (i.e. spontaneous use of skills in new settings) required for good functional outcomes is more rare (25, 26). Challenges in generalization of learning extend beyond ASD into developmental disabilities more broadly. As posited by the "Piagetian argument that an instructional experiment has not influenced intelligence until it has changed a wide range of uninstructed behaviors as well as instructed ones" (27), failure to generalize new learning is a transdiagnostic threat in developmental disabilities that leads to wasted resources on treatments that do not change behavior in real world settings. Treatment research in ASD has been slow to address this problem, as many clinical trials do not investigate distal generalization of findings, and those that do typically do not find evidence for it (11, 13, 26, 28). The sobering reality is that despite attaining significant insight into the behavioral, neural, and genetic bases of ASD, our ability to help autistic people independently adapt to their environments, and demonstrate learned social skills remains limited, (23, 29) and their health, employment, adaptive, and quality of life outcomes remain poor (30-36).

**Executive functions (EF), particularly the EF subdomain of flexibility, are impaired in ASD.** EF is a set of functions that enable people to strategically regulate thinking and behavior in the service of goals. EF abilities include flexibility, organization, working memory and planning, each of which is deficient in ASD as reported in a series of reviews over the past few decades (37-40), including our own (41). Two recent meta-analyses involving thousands of children identified flexibility, generativity, and working memory impairments as "core EF deficits" in ASD (39), and indicate that EF problems are significant (i.e. moderate effect size) and stable across development (42). Among the EF subdomains impaired in ASD, inflexibility has been identified as the hallmark. A quantitative review of 72 studies found that self- and parent-report of inflexibility robustly discriminated between individuals with ASD without ID and those with TD. A meta-analysis of 31 studies regarding a common marker of cognitive inflexibility, the perseverative errors score on the Wisconsin Card Sorting Test, confirmed increased perseveration in ASD (40). Contrary to speculation that the social interaction required by the task compounds flexibility problems, individuals with ASD had similar difficulty with flexibility whether the task was administered by a computer or a person. We conducted a large factor analysis of parent-reported EF problems in children with ASD without ID which identified flexibility problems as a key driver of EF deficits in multiple domains (43).

**EF, and flexibility in particular, is related to weak generalization of skills and poor outcomes in ASD.** It is difficult to spontaneously transfer previously learned information to new settings, and use it flexibly to generate appropriate behaviors without recourse to EF. Training in EF strategies has been proposed to promote skill generalization (44, 45), and, conversely, flexibility deficits have been linked to generalization problems in ASD (12, 38) and in early development among TD youth (46). The combination of inflexibility and difficulty organizing information into a unified whole (47) leads to a strong tendency to get stuck on details at the expense of integrating information. Not surprisingly, EF is also linked to key outcomes in ASD, many of which rely on the capacity to demonstrate learned skills in new unstructured settings. EF problems and inflexibility predict reduced: quality of life (36, 48), academic achievement (49, 50), and social skills (49, 51, 52). Adaptive behavior, including social, communication and daily living skills, is key to independence as an adult. The unexpectedly large gap between intelligence and adaptive skills in individuals with ASD without ID is a measure of the challenges they face generalizing their knowledge to real world settings and demands. In cross-sectional and longitudinal studies, we have shown that the inability to transfer knowledge into functional adaptive skills is related to EF and flexibility (31, 53, 54).

## 2.2 Scientific Rationale

### SPECIFIC AIMS & HYPOTHESES

**Aim 1. *Activation and behavior at baseline:* Learning bias (exemplar/prototype) varies among ASD youth, is associated with flexibility, and is stable over time.** Learning categories from feedback, followed by generalization to new exemplars will be examined during fMRI. At both T1 and T2, stronger prototype bias (higher prototype than exemplar model fit) and greater vmPFC activation will be associated with better flexibility and adaptive behavior. Learning bias will be stable between T1 versus T2.

**Aim 2. *Intervention effect on activation and behavior: UOT* in ASD leads to increased prototype-based learning and vmPFC activity.** At T3, ASD youth will exhibit stronger prototype model fit, flexibility and adaptive behavior, than T2, and vmPFC activation will be positively associated with UOT behavioral response.

**Aim 3. Resting-state functional connectivity (rsFC) and behavior: Heterogeneity in learning biases and change in response to *Unstuck* will be associated with rsFC.** vmPFC-MTL rsFC and MTL network strength will be associated with prototype learning and response to UOT.

**Rationale of the present proposal: Flexible generalization of learning requires abstraction**

**Our overarching hypothesis is that learning mechanisms that promote flexibility are atypical in ASD.** Learning to abstract common elements (e.g., category learning) or hierarchies (e.g., rule learning) enables adaptation to novel settings, thus fostering flexible behavior. Further, abstraction provides the structure for implementing flexible control, such as switching task-sets (4). Our premise is that rigid behavior in ASD is the outcome of faulty learning mechanisms of abstraction. Learning mechanisms are plastic, and therefore, if an intervention is successful in increasing behavioral flexibility, we ought to observe concomitant changes in the learning mechanism in the brain. Our cognitive-behavioral intervention (*Unstuck and On Target* - UOT, elaborated later) is effective in improving behavioral flexibility in autistic youth (15, 55, 56). We test our prediction by focusing on one potential mechanism of abstraction: *category learning,* (57) because a key component of UOT is emphasis on integration across experiences and creating flexible, abstract prototypes through extensive, explicit and repetitive practice applying specific exemplars to categories of experience. Other elements act directly on modeling flexible behavior in the real world. Our prediction is that the observed behavioral change following UOT is rooted in plasticity of category learning. We think understanding the nexus of EF and learning likely holds the key to resolving the generalization challenge in ASD, an area that has received little attention. Our results will identify potential neural markers of treatment sensitivity and response.

**Our project leverages the *Neuroimaging, Neurobehavioral and Clinical Translational Cores* and the Project Directors' complementary expertise. It capitalizes on our effective EF intervention to examine neural plasticity in ASD. It fills a significant gap in ASD research (58) and responds to RFA themes:** *Interventions and Management of Co-morbid Mental Health Conditions and* ***Outcome Measures or Biomarkers for Interventions or Treatments, and to the DC-IDDRC theme of Neural Development and Neurodevelopmental Disorders.***

**Potential mechanism: Category learning**

**Building categories by abstracting common elements promotes flexible adaptation to novel settings and generalization of learned skills.** Categorization of objects, actions, and events is one of the earliest mechanisms by which teens learn about the world (59). Categorical knowledge is further built into more abstract schematic frameworks that foster flexible adaptation to unpredictable environments. Organizing experiences into categories is accomplished by integrating common elements into summary or average representations, termed *prototypes* (60). Observed as early as infancy, prototype learning allows for interpreting new and unpredictable information, which simplifies the environment because it does not rely on remembering separate details or events. Further, it fosters flexibility in adapting to varying environments because new instances or events can be rapidly mapped onto an existing *similar* blueprint, providing a roadmap for action. The social world lends itself particularly well to this learning process because it is complex and unpredictable (61). Perceptual processing is foundational to this type of learning because the first step to categorizing is *noticing* relevant features (57). Thus, a poodle and chihuahua are recognized as "dog" whether in the park or in a cartoon because they share features with a prototypical dog (four legs, fur, tail, barks), even though each *exemplar* of dog differs in shape and actions. In the brain, prototypes and schemas are represented by ventral medial prefrontal cortex (vmPFC) (7, 8, 19, 62, 63). At the same time that prototypes are generated, the brain maintains information about specific exemplars such as the poodle and the chihuahua in the park versus the cartoon. Exemplar-specific learning is useful for certain goals and contexts (e.g., recognizing that the same poodle comes to the park everyday), but it does not promote flexible adaptation to new environments. Such specific representations are coded by the hippocampus in the medial temporal lobe (MTL), with variation along its long axis, with feature-specific details represented posteriorly and gestalt anteriorly (64). Thus, from vmPFC to anterior and posterior MTL, a gradient of abstraction represents the building blocks of category learning.

**"Over-specificity" in ASD leads to weakness in generating prototypes.** In his original description, Kanner identified the "inability to experience wholes without full attention to the constituent parts" (65), and later, Rimland (21) linked generalization problems in ASD to specificity of memory and limited integration of information. Since then, "hyper-specific representations" (66), and highly detailed processing is thought to be prototypical of ASD and related to problems with generalization of knowledge (47, 67-69). Indeed, a perceptual processing bias favoring details (termed weak central coherence (70)) that promotes "over-specificity" (71, 72) has been posited to limit formation of abstract representations in ASD (73). Such enhanced perceptual discrimination abilities lead autistic individuals to perceive similar stimuli as dissimilar, and focus on differences rather than similarities among objects, resulting in weak categorization and generalization (68). Prioritizing specificity and detail over integration and "gist", may lead to weak prototypes resulting in poor generalization and difficulty adapting to new environments. This in turn may create a preference for sameness, which is likely to limit seeking of novel experiences, leading to further weakening of prototypes. Indeed, stimulus repetition limits perceptual learning and generalization in TD (74) and reducing stimulus repetition eliminated over-specificity in ASD (71).

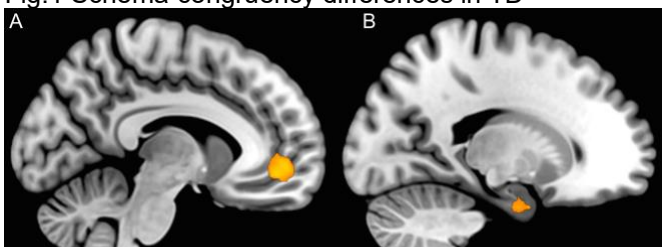
**Aim 1: Hypothesis – Reliance on learning exemplars undermines category learning in ASD**

**Studies of category learning in ASD show high heterogeneity among individuals (18).** Tasks used include a training phase with feedback for learning to classify exemplars of artificial stimuli (e.g., dot configurations, artificial stimuli varying in features) into categories (e.g., A/not-A or A/B categories) followed by a generalization phase during which novel unseen exemplars are presented for classification. In studies using dot configurations, some autistic individuals showed slower learning during training and reduced generalization to new exemplars (75). In other studies, subgroups showed intact generalization whereas others were impaired (66, 76). Why some autistic teens form prototypes and generalize whereas other don't, cannot be explained by differences in stimuli/task, age, or training regimen; ASD etiology has not been manipulated or reported in these studies. Connectionist models explain this heterogeneity as differences in neural plasticity (77), and findings support their prediction that atypical learners will benefit from extensive training on a single prototype stimuli (rather than exposure to multiple exemplars) (78). Such training may drive neural plasticity by enhancing prototype-based mechanisms. However, no study has examined such neural plasticity in ASD.

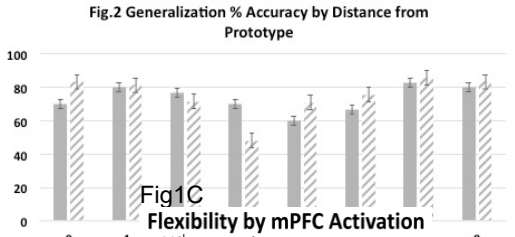
**Strong rote learning skills in ASD may promote learning of individual exemplars** (58). On a set of four feature artificial stimuli, autistic children were unable to classify new stimuli by generating a prototype, however they successfully classified new stimuli by learning an explicit one-feature rule (73). Using the same stimuli, autistic children demonstrated accurate recognition memory for stimuli that were similar to learned exemplars (79). In another study, autistic adults false alarmed to exemplars that were similar to training exemplars on a recognition memory (80). Thus, autistic children remember individual exemplars but cannot integrate across them to form generalized representations.

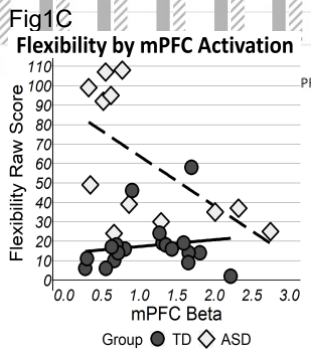
**Findings reviewed above lead to our hypothesis that the observed heterogeneity in ASD reflects variation in the extent to which learning relies on exemplars or prototypes.** Cognitive models of category learning in psychology have applied computational modeling to predict how novel exemplars are being classified by each *individual*, whether based on similarity to training exemplars or similarity to a prototype representation (81, 82). Recently this model-based approach has been extended to neuroimaging by Zeithamova and colleagues (8, 83) and others (84). The present study adopts these methods (see consultant letter from Dr. Zeithamova), which provides model-fit parameters for exemplar and prototype learning, which can be compared statistically to determine the stronger mechanism in that individual. Further, these model parameters are used as regressors in fMRI data acquired during generalization performance, to identify associated neural correlates, i.e., brain regions whose activation profiles are predicted by the learning model's algorithm (85, 86). This novel model-based fMRI (m-fMRI) approach has shown that prototype learning in TD adults engages vmPFC (8), whereas exemplar-based learning engages hippocampus in MTL and additional lateral occipital, inferior parietal, and inferior frontal regions. **Application of this individualized model-based approach allows for examination of individual variation in the strength of learning mechanisms, their plasticity, and testing predictions about associated neural correlates.**

Fig.1 Schema-congruency differences in TD



**Preliminary data below 1) shows schematic encoding-related mPFC recruitment relates to variability in behavioral flexibility in ASD; and 2) establishes the feasibility of our approach to reveal variability in learning bias for the proposed category learning task in youth with ASD.**




1) We examined neural correlates of subsequently remembered object-scene pairs that varied in congruency to conceptual schemas (congruent, intermediate, incongruent) in 19 8-15 year-old TD and 12 age-matched autistic teens. Schema-congruency differed significantly in vmPFC (Fig. 1A) and left anterior MTL (Fig.1B) in TD teens (one-way voxel-wise ANOVA, p<.05 corr) but not in ASD, although higher parent-reported inflexibility related to lower mPFC in ASD (Fig.1C open diamonds r=-.61, p=.03 with apriori mPFC ROI from Fig1A). Variability in flexibility is apparent even in this small sample, suggesting that the proposed N=54 will have sufficient heterogeneity to probe activation differences.
2) We tested 6 TD and 5 autistic teens 12-14 years using the same category-learning task and analysis as described in Approach (*covid-19* closures prevented further data collection). We deliberately tested younger ages than proposed, to test the feasibility of the protocol. Training accuracy was greater than chance (50%) in all youth and generalization accuracy was higher for novel exemplars sharing more features with prototypes (Fig.2 #1,2,6,7 on x-axis). Model fitting showed that 1 ASD youth did not show significant fits for either prototype or exemplar ("random"), and of the remaining, permutation testing showed that 2 were stronger for prototype and 2 for exemplar (model fit range: 18-44). fMRI of these 4 subjects (others were not imaged) showed that the 2 regressors revealed good range of beta estimates (rounded) in the regions of interest for both regressors: vmPFC (27 to -18), anterior MTL (16 to -12), and posterior MTL (13 to -9). Thus, it is feasible to use this approach to probe heterogeneity in ASD.

**<u>Aim 2: Hypothesis – Baseline prototype learning predicts treatment response *and* UOT promotes plasticity of prototype learning</u>**

***UOT* (87) is a 24 lesson cognitive-behavioral EF intervention designed to increase independent flexible problem-solving, goal-setting and planning in transition-age autistic youth without ID.** It is an upward extension of *Unstuck and On Target-Elementary School (UOT-ES)*, an EF intervention for 7-11 year olds, which has been shown to be effective in two large scale trials (15, 56) and is rated as having the highest tier of quality by the Agency for Health Care Research (88). UOT preserves the teaching techniques and intervention model of the UOT-ES while adjusting the content for 14-18 year olds. UOT combines specific neurocognitive targets of treatment (e.g., flexibility, goal setting, planning) and evidence-based teaching practices for autistic learners (e.g., use of scripts, modeling, visual supports) (89). The intervention uses 'supported cognition' techniques to leverage cognitive strengths and support cognitive weaknesses common in ASD and other DD's associated with poor EF (90). ***Instruction aims to generate prototypes with: 1) presentation of many examples with consistent, explicit linkages to overarching concepts and goals; 2) use of a repetitive, common language (scripts) at home and at school to build the category of flexibility and schema for what flexible behavior looks like in everyday settings; and 3) direct instruction in 'big picture' thinking versus detail focus. UOT supports spontaneous generalization through: 1) metacognition skills (e.g. promotes awareness of strengths and weaknesses, and the value of big picture goals and flexibility); 2) engagement of parents and teachers to increase 'dosage' of treatment, and 3) practicing scripts and skills to automaticity* (44, 45, 91).** Scripts include: 'stuck on a detail', 'eyes on the prize', 'PlanA/PlanB', and 'Goal Why Plan Do Check'. Community based participatory process during intervention development maximized implementation feasibility and stakeholder acceptability. Treatment content was iteratively refined in clinic and school settings based on stakeholder feedback and reviewed by the Autistic Self Advocacy Network (55, 92, 93).

**Preliminary data on effectiveness from three RCTs demonstrates that UOT improves flexibility, but there is heterogeneity of response**. The elementary school version of UOT (UOT-ES) has been tested in two randomized effectiveness trials, one for children with ASD only and the second for children with ASD or ADHD. Both trials compared UOT-ES to equal doses of an established treatment. In the first trial, children in UOT-ES showed greater improvement in flexibility and problem solving efficiency

on masked outcome measures, and greater generalization of executive function skills to home and classroom settings then children receiving the comparator treatment (15). In the second trial treatment response at the individual level was probed. Significant improvements at the group level with medium to large effect sizes were nonetheless associated with variability in treatment response at the individual level, with some children identified as non-responders in this trial (56).

**A third RCT examined the impact of UOT on high school student outcomes**. Six schools were randomized to UOT (N=35) and four to treatment as usual (TAU; IEP services, ASD/EF supports already in place; N=20). Participants were 55 9th-12th graders (9 females, *M* age=16.44, *SD*=1.21) with ASD, possessing IQ ≥ 80 (*M*=103.49, *SD*=15.69). UOT was provided by teachers during school class-wide or in pull-out groups. Parents received two 1-hour training sessions and a manual for skill generalization. Intervention impact was assessed across settings (home, school, laboratory), at endpoint and at 6 month follow-up for the following outcomes. 1) Flexibility: The EF Challenge Task (EFCT) (94) Flexibility score, and Behavior Rating Inventory of Executive Function-2 Shift subscale (BRIEF-2, parent-report). 2) Distal Generalization: Classroom learning behaviors were coded during 15 minute observations in non-intervention academic classes by a treatment-masked research assistant. Parents reported on adaptive behavior using Adaptive Behavior Assessment System-3 (ABAS-3).

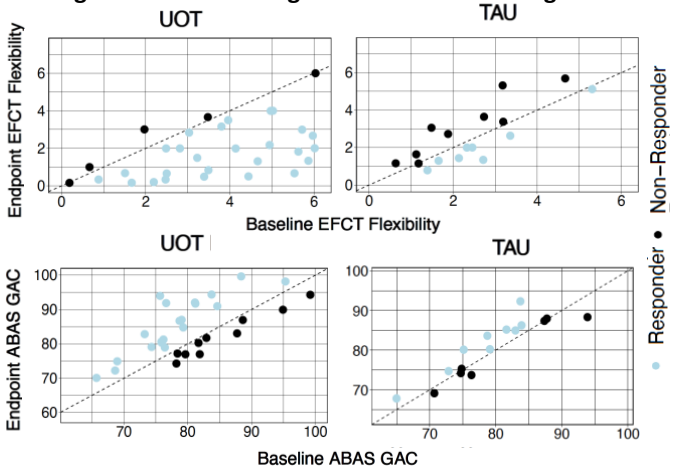
**Table 1: Effect Sizes for Group-Level Improvement in UOT compared to TAU**

| | Instrument | Pre-Post ($\eta_p^2$) | Pre-Follow Up ($\eta_p^2$) |
|---|---|---|---|
| **EF Targets** | EFCT: Flexibility | **0.28*** (large)** | 0.01 (small) |
| | BRIEF: Shift | **0.09* (med)** | 0.06 (med) |
| **Outcomes** | Classroom Behavior | **0.12* (med-large)** | ---------- |
| | ABAS: Global Adaptive Composite | **0.13* (med-large)** | **0.19*** (large) |

$\eta_p^2$=partial eta squared; *$p$<.05;**$p$<.01;***$p$<.001

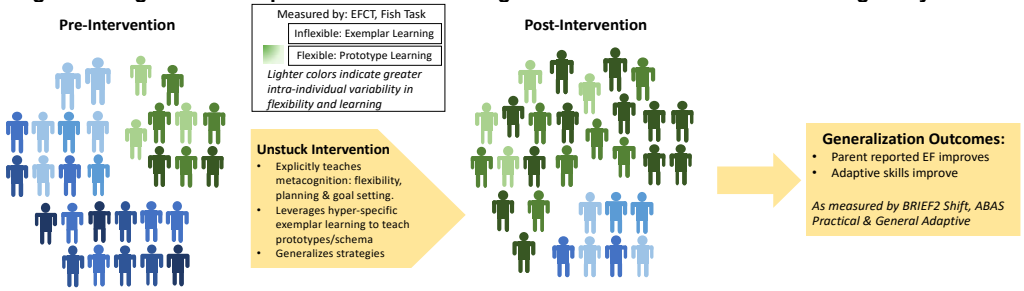
**Compared to TAU, UOT resulted in better post-intervention scores on flexibility, with distal generalization to classroom behavior, and adaptive skills at home** (see Table 1 for effect sizes). Controlling for baseline scores and IQ, the UOT group had significantly better task-based and parent-reported flexibility skills (EFCT: $F_{1,49}$=17.66, $p$=.00; BRIEF-2: $F_{1,49}$=4.24, $p$=.045), and distal real-world outcomes: classroom behavior ($F_{1,53}$=6.22, $p$=.01) and global adaptive skills ($F_{3,53}$=6.76, $p$=.01) post-intervention than the TAU group (92, 93). Although underpowered to detect effects at one-year follow-up, the UOT group had significantly better adaptive scores from baseline ($F_{1,\ 36}$=7.37, $p$=.01) and non-significantly better scores on parent-reported Flexibility corresponding to a medium-effect size (classroom observations not conducted). Improvement on EFCT Flexibility directly related to improvement in observed classroom behavior from baseline to endpoint ($r$=-.34, $p$=.02). While group-based UOT related improvements were clear, non-responders (i.e., scores remain the same or decline following intervention) were observed on key outcome measures, as demonstrated in Figure 3, which shows pre- versus post-scores for participants receiving UOT or TAU. 47% of the UOT and 0% of the TAU groups showed postive reliable change on the EFCT Flexibility score following intervention. As is commonly seen in intervention studies, **pre-intervention outcome scores significantly predicted scores at post-intervention**, (EFCT Flex pre-score predicted post-score (p<.001, $\eta_p^2$=.18).

**Fig. 3 Individual Change in Outcome Following UOT**




In this study we will evaluate improvement in, and generalization of, flexibility skills learned during UOT and examine whether pre to post-intervention behavioral change is associated with change in learning model-fit parameters (see Fig. 4). We will use a case-controlled

**Figure 4. Logic Model: Impact of UOT accounting for intra- & inter-individual heterogeneity**



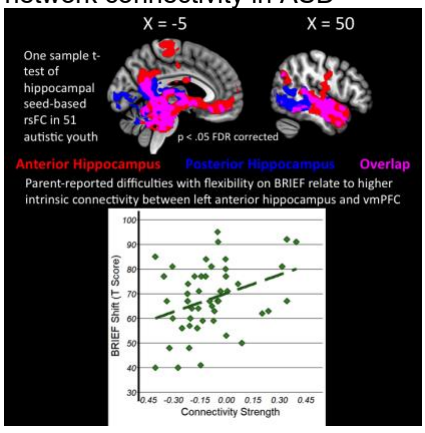
design and individualized computational models of learning in order to probe for differences in cognitive profile among autistic participants that may inform differential treatment response. We predict that those with pre-intervention learning biased towards exemplars (blue in model) will change their learning bias to prototype generation post-intervention; the subset with prototype bias pre-intervention will become stronger in that bias post-intervention (darker green in model). We aim to bridge the gap between well-defined computational cognitive learning tasks and real world functioning in adolescents, for whom spontaneous transfer of learned skills into novel everyday settings is fundamental to positive adult outcomes. Our method expects and probes heterogeneity in EF and learning within and between the autistic participants. We expect some treatment non-responders, and will explore whether they represent a subset with extreme scores in terms of EF (flexibility), learning (prototype, exemplar) or neural response. Heterogeneity in response to treatment is a fundamental target of inquiry in ASD, as identifying how a subset of autistic children learn and generalize new skills would enable an individualized approach to treatment.

**Aim 3: Hypothesis – mPFC-MTL intrinsic functional connectivity (FC) will be associated with prototype learning and show UOT-induced plasticity**

**FC during the task-free, resting state, reflects the baseline network architecture of the brain.** Functional brain organization revealed with task-evoked activity parallels what is observed in spontaneous neural activity, measured while one is not engaged in a directed task (termed resting-state) (95). Task-evoked and resting modalities provide complementary information – evoked studies visualize properties of a *deployed* process while resting-state studies visualize the *potential* for that process, revealing the baseline functional architecture, termed *intrinsic networks.* Such FC, identified by temporo-spatial correlation in neural activity at low frequencies (< .05 Hz), is stable across individuals (96) and reflects neuronal activity rather than physiological noise (97).

**vmPFC and MTL are part of a subnetwork of the default mode network (10), engaged in memory integration, that has received little attention in ASD.** The functional connection between vmPFC and MTL has been emphasized in enabling abstract representation, such that inhibition of exemplar-specific encoding in MTL by vmPFC facilitates prototype/schematic representation in vmPFC (7, 98, 99). In addition, lateral parietal cortex has also been implicated in schematic representation (100). These regions are part of a larger functional network, termed default mode network (DMN) after the observation from PET studies that select regions are more metabolically active than any others in the resting state (101). DMN regions include midline mPFC and posterior cingulate cortex (PCC), MTL, including parahippocampal and retrosplenial regions, lateral parietal cortex, and temporal lobe. A large literature has coalesced to suggest that the DMN is involved in autobiographical (past, present, future) and socially referential thinking (102). Andrews-Hanna et al [10] demonstrated a functional decomposition of the DMN into two subsystems, 1) MTL subsystem (vmPFC and lateral parietal cortex, see Fig. 5) subserving episodic *past and future-oriented* thought, specifically "construction of a mental scene based on memory", and 2) dorsomedial PFC subsystem (connections to temporal pole, lateral temporal cortex, and temporoparietal junction) subserving self-referential *present-oriented* thought. Both subsytems connect to the midline core, anteromedial PFC and PCC. While numerous studies including ours (103) have shown that the midline core is under connected in autistic adolescents, other nodes show a mixed pattern of under and over connectivity in autistic relative to TD children (104)). **No study has focused upon the status of the MTL network in ASD. We predict that MTL-vmPFC and whole-brain MTL subnetwork FC will reflect prototype learning variability and UOT-induced change. These results will show that UOT changes baseline learning architecture.**

Fig. 5 MTL-vmPFC intrinsic network connectivity in ASD




**Our preliminary data establish atypical MTL network intrinsic FC in ASD and association of MTL-vmPFC FC with parent-reported flexibility in autistic youth.** In past work we have extensively demonstrated that atypical intrinsic FC explains individual variability in ASD symptoms and EF (103, 105-107). In a preliminary study, we delineated the MTL network in 8-14 year-old 51 autistic children using whole brain voxelwise FC using left and right anterior and posterior hippocampal seeds (color-coded on Fig. 5) processed as described in Imaging Analysis. The same MTL subsystem nodes as reported by (10) are observed, including vMPFC and lateral parietal cortex, in addition to the midline core, PCC. **However, MTL showed FC with lateral temporal and temporal pole, which is nominally part of the dorsomedial PFC subsystem, suggesting a lack of**

**segregation of the MTL sub-network in ASD.** Indeed, comparison with an age-matched TD sample (not shown here) confirmed the MTL-lateral temporal hyper-connectivity. Further, MTL-vmPFC connectivity was associated with flexibility indexed by BRIEF Shift domain scores, *r*=.40, p=.03 (scatterplot in Fig. 5). **This effect size was used to determine the sample size for the present study.**

## 2.3 Potential Risks

*Behavioral tasks and Treatment Trial*: The physical, legal, social, and psychological risks involved in this study are minimal. Teenagers and parents may feel uncomfortable answering some questions and some participants may not like the activities in the intervention. All questions and activities will be developmentally appropriate. Participation in the diagnostic and cognitive assessments may be boring or anxiety provoking. To minimize this risk, all assessments will be conducted by trained psychologists or research assistants under the direct, on-site supervision of a psychologist trained in working with teens with ASD (except for the ADOS, which will only be administered by trained, research-reliable license-eligible/licensed clinicians). Participants may opt to withdraw from individual tests or intervention treatment or the entire protocol at any time. The results of treatment and testing will be protected under HIPPA statutes and will be provided to the participant for their own knowledge but will be kept out of their medical records.

*fMRI tasks*: The risks of fMRI studies are no greater than minimal risk when proper procedures are followed. Studies involve a 3.0 Tesla MR scanner, which conform to FDA safety guidelines. Such scanners are available for patient studies at other major medical centers and have been used for a number of years without problems. MRI has been performed on teenagers for over 30 years, (fMRI for over 20 years) without ill effect or discomfort. Teen's heads will be immobilized in the scanner (with custom head stabilizers https://caseforge.co/), and this may be minimally uncomfortable. Sedation will not be used during any portion of this study. There are no known biological risks due to exposure to magnetic fields from MRI exams using techniques such as those that will be utilized in this study. There is a potential risk of the main magnetic field attracting ferromagnetic objects toward the magnet. This risk is minimized by careful screening of study participants prior to entry into the magnetically shielded room. Study participants may experience some discomfort associated with the noise of the scanning. This is minimized by use of earplugs and sound padding over the ears. Anxiety and discomfort may be experienced from lying in the magnet during the scan. To address these problems, potential study participants will be screened for claustrophobia during recruitment. Participants can practice with a deactivated mock scanner prior to the MRI testing that will simulate being in the MRI scanner prior to the MRI testing. The MR technologist will regularly provide information about the progress of the examination and there is opportunity for communication during the procedure with the technologist. The study participant may abort the examination at any time. Time spent in the magnet will not exceed 60 minutes and participants can refuse participation at any point during the scan. Participants will be allowed to participate in the rest of the study if they cannot be scanned or refuse to be scanned.
Participants who are on stimulant medication will withdraw medication for at least 24 hours. Potential risks from withdrawing stimulant medication are minimal. They include return of symptoms of inattention, hyperactivity and impulsivity. It is common and at times, preferred medical practice to routinely withdraw medication in ASD youth during nights, weekends (48 hours), for school vacations (1-2 weeks), and for summer vacations (2-3 months). Most of our scanning is done on weekends. There is no risk associated with withdrawal or restarting stimulant medications. All other medications and non-medical treatments will be administered as usual.

**Confidentiality of study data**: Loss of participant confidentiality is extremely unlikely, but it is a potential risk. We have developed systematic protocols for data handling and storage over multiple studies, and only de-identified data with no PHI will be shared across sites.

- **Disclosure:** The consent/assent forms will contain both the required elements of consent (listed above) as well as the required HIPAA language. The disclosure will note that researchers will do their best to keep participants' personal information private and confidential, but that absolute confidentiality is not guaranteed. This research project is part of a family-based intervention so

participants will be informed that information will be shared with parents about the child's progress as well as any if there are concerns about harm.

- Participants' personal information may be disclosed if required by law and a list of people/organizations that may inspect and/or copy research records to assure quality of the data (e.g., members of the research team) will be provided. The disclosure will also note that study results may be shown at meetings or published in journals to inform other health professionals, but that participants' identity will never be revealed in publications or presentations about the study.
- **Deidentification of data:** Participant names will be obtained during the consenting process but these will only be logged once and stored in a single location at time of initial contact. Each participant will be given a unique alphanumeric identifier (no names or other identifying information) upon enrollment and data will only be identified by this identifier. Thus, although we will know who participated (and this will be held in strict confidentiality), it will not be evident which results/data belong to which individual. De-identified data will only be examined by trained, authorized research professionals affiliated with the project with the permission of the PD. The research team will be informed that disclosure of confidential information is grounds for termination.
- **Data entry, storage, and sharing:** Any "hard copy" data will be assigned the alphanumeric ID and stored at the Center for Autism Spectrum Disorders at CNH in a locked in a filing cabinet in a secured office separate from any identifying information (e.g., names, student or patient IDs, addresses, phone numbers, consents/ assent forms). Only members of the immediate research team will have access to the files which are maintained in locked office. All data will be scored on CNH computers that are password protected and located in locked private offices, and with software that require additional access codes. Data will also be entered on a password-protected CNH computer, and managed using Research Electronic Data Capture (REDCap) software hosted at Children's National. REDCap includes a complete suite of features to support HIPAA compliance (e.g., audit trail, user-based privileges, secure sockets layer encryption, etc.). Data files will be password protected behind a hospital maintained firewall. Access to the study's data in REDCap will be restricted to the members of the study team by username and password. Data will be de-identified when exported for analysis. Consistent with IRB policies, data shared with statisticians will be de-identified and contain no PHI. Information shared about study findings will be presented in aggregate with no personally identifiable information attached to it. At the end of the study, all study databases will be archived at CNH and maintained for 10 years.

**Protection Against Risk**

*Behavioral tasks and treatment groups:* Regarding the behavioral and cognitive assessment, testing will not begin until the participant is comfortable with the environment and the tester. Each tester will be attentive to study participant fatigue and will provide breaks as needed and adjust the length of the test sessions to each individual (*e.g.,* longer breaks, two sessions, etc.). Study participants will be provided with frequent positive feedback. Only designated project staff will be allowed entry to the room. Utmost care will be taken to avoid breaches of confidentiality. Interventionists and study personnel will emphasize that all information discussed during treatment groups and parent trainings should be kept confidential by participants and parents. However, there is the chance that participants or parents may share information outside of the treatment groups or trainings. See Data Safety and Monitoring Plan for plan to manage adverse effects.

*fMRI tasks:* MRI/fMRI has been utilized in teens and adults, with minimal ill effects or discomfort for over a decade when safety guidelines are strictly enforced. The FDA has concluded that a magnetic field below 4.7 T does not by itself impose a risk to human study participants and has approved the use of magnetic field strengths of up to 4.1 Tesla for MR scanning of humans in a research environment. Regarding MRI acquisition, risks will be minimized by giving study participants and their families ample opportunity to tour the MRI facilities, observe ongoing MRI scanning, and undergo acclimatization in the mock scanner. Based on prior experience, ill effects during fMRI are uncommon because we take the time and effort to educate and prepare participants. Rehearsal runs will be performed to habituate study participants to scanner conditions. Study participants will wear pneumatic earphones designed to minimize scanner noise. We will show the study participant's favorite video while they are in the scanner when paradigms are not being performed. Any study participant who does not tolerate mock or test conditions will be removed from the scanner and the protocol. A participant's parent or a member of the research staff may accompany them for the entire duration of the MRI scanning, if desired.

Prior to entering the MRI suite, a metal detector will be used to check for metal on the study participant and parent's person. Two personnel at the Center for Functional Magnetic Imaging at GU will follow protocol to ensure that participants are not wearing metal. Study participants may ask to stop the MRI exam at any time. Metallic devices are not allowed in the MRI area; all MRI study participants must remove all metallic devices before entry into the scanning suite. We will go to great lengths to assure that the study population is comfortable in the scanning environment. We will provide a picture of the scanner at the initial visit and a tour of the scanner/console rooms before beginning the imaging session. A parent or guardian may accompany the participant at all times in the scanner or scanner control room (if they are medically safe to be in the scanner environment). Our view is that the study should be a fun, educational experience for all of the participants. Information about how the study helps increase our understanding about ASD will be shared with the study participants and their families to give them a sense of how they are contributing to science and helping transition-age youth with ASD. Participants will receive a picture of their brain at the end of the scanning session. If a medical condition or learning disorder is identified during the study, an appropriate referral will be made.

In the event of unexpected anatomical abnormalities spotted on the MRI by scanning technicians or PI/staff, we will follow CFMI procedures for appropriate referral. This procedure is that Dr. Van Meter (Director of CFMI) shows the scan to the neurologist affiliated to CFMI (Dr. Peter Turkeltaub), and his opinion is communicated to the family (parent or guardian signing the consent form) or adult participant by the PI; appropriate referrals are made. Accordingly, PD Vaidya will follow these procedures. MRIs are not routinely read for abnormalities at CFMI because acquisition parameters used are not optimized for revealing clinical information.

### 2.4 Potential Benefits

It is vital to study adolescent youth with ASD because this remains a critically understudied population in the field. This research has value in its: 1) contribution to the evidence base regarding effective treatments for executive dysfunction in youth with ASD; 2) potential to identify factors that will predict treatment response; and 3) potential to identify *mechanisms* of response to treatment and generalization of skills in the brain. This study is designed to add to this knowledge base and could improve general understanding regarding effective treatment of executive dysfunction in youth with ASD and other DDs. We do expect some participants to benefit from the treatment offered, based on preliminary evidence of effectiveness. Findings from behavioral assessment procedures will be made available to families upon request and may be helpful for some participants' clinical/education planning. If a medical condition or learning or psychological disorder is identified, an appropriate referral will be made. Participants will be reimbursed for their efforts according to IRB policy, and may withdraw from the study at any time.

## Section 3: Objectives and Endpoints

### 3.1 Objectives

The proposed project aims to elucidate the association between learning and flexibility by testing whether intervening to promote flexible behavior in ASD changes learning and associated neural mechanisms.

**Aim 1. *Activation and behavior at baseline:* Learning bias (exemplar/prototype) varies among ASD youth, is associated with flexibility, and is stable over time.** Learning categories from feedback, followed by generalization to new exemplars will be examined during fMRI. At both T1 and T2, stronger prototype bias (higher prototype than exemplar model fit) and greater vmPFC activation will be associated with better flexibility and adaptive behavior. Learning bias will be stable between T1 versus T2.

**Aim 2. *Intervention effect on activation and behavior: UOT* in ASD leads to increased prototype-based learning and vmPFC activity.** At T3, ASD youth will exhibit stronger prototype model fit, flexibility

and adaptive behavior, than T2, and vmPFC activation will be positively associated with UOT behavioral response.

**Aim 3. Resting-state functional connectivity (rsFC) and behavior: Heterogeneity in learning biases and change in response to *Unstuck* will be associated with rsFC.** vmPFC-MTL rsFC and MTL network strength will be associated with prototype learning and response to UOT.

### 3.3 Primary & Secondary Outcome Measure(s)

Use of prototype or exemplar based learning will be evaluated with a validated task and computational modeling. Proposed measures of flexibility and adaptive behavior have been iteratively tested and refined across four pragmatic school-based EF intervention RCTs (15, 55, 56, 93, 94) and have shown sensitivity to treatment change. Multi-modal measures will be collected to assess flexibility as a correlate of neural activity and a mechanism of learning and change in response to treatment. Distal generalization will be evaluated with a measure of adaptive behavior. To the extent possible, research staff masked to timepoint (i.e. whether the participant has received the intervention yet or not) will code the EFCT from video recordings.

**Executive Function Challenge Task (EFCT; 94)** (see Appendix) is a standardized objective measure that assesses flexibility and planning in the context of 4 interactive tasks (e.g. examiner and participant complete a drawing together, examiner challenges participant to be flexible by making errors, and codes participant's response). It can be coded reliably, has 2 parallel forms, demonstrates adequate reliability and validity, and has a two-factor structure (Flexibility and Planning). Unpublished data indicates acceptable (.76) internal consistency in adolescents. Higher raw scores for flexibility, planning and total EF, indicate more problems. It has been sensitive to UOT in all previous trials and is our primary outcome.

**Behavior Rating Inventory of Executive Function (BRIEF-2; 119)** is a well-established parent-report measure of real-world EF skills. The Shift subscale measures flexibility (ability to move freely from one situation, activity, or aspect of a problem to another as the situation demands; problem-solving flexibility). It has good internal consistency (.86) and test-retest reliability (.77). Performance is represented as T-scores (mean=50; SD=10), with higher scores indicating more problems.

**Adaptive Behavior Assessment System (ABAS-3**; 120) is a well-validated parent report measure that assesses practical, everyday skills needed to effectively and independently take care of oneself and interact with others across the lifespan. Estimates of internal consistency and test-retest reliability are above .90 and inter-rater reliability is also high (.91-.99)(120). Factor analytic, concurrent validity and clinical studies provide strong support for its validity. Performance is represented as standard scores (mean=100; SD=15), with higher scores indicating better adaptive skills.

**The Category Learning Task** is an A/B categorization task that begins with an out-of-scanner training phase during which participants learn to classify exemplars of cartoon stimuli into two "families" through feedback followed by an in-scanner generalization phase during which novel unseen exemplars are presented for classification. Three different stimuli sets (Fish, Butterflies, Bugs) will be used for the three timepoints, with stimuli counterbalanced across participants (Fish Task was used in preliminary data and is described below, which is paralleled for the Butterflies and Bugs Tasks). These tasks were modeled after studies of Ziethamova et al (8, 83) using cartoon fish (Fig. 6) that differ on eight binary dimensions: eye shape (triangle/circle) body shape (square/oval), tail shape (pointy /curvy), body markings (stripes/scales), top fin shape (curvy/boxy), bottom fin shape (triangle/lightning bolt), mouth (lips/open mouth), and antenna (presence/ absence). One stimulus is chosen randomly from a set of four possible prototypes to be the prototype of category A ("Mip" family). The stimulus that shares all the opposite features with the category A prototype serves as the category B prototype ("Nax" family) (see Fig 6 for examples - #8 is Protoype A and #0 is Prototype B and the adjoining three exemplars represent distance away from prototype in features such that #7 differs from the prototype A by one feature (body shape), #6 differs by two features (eye shape, fin shape), and #5 differes by three features (mouth, eye, dorsal fin). Thus, physical distance between all stimuli is defined based on the number of differing features. Mips

shared more features with Prototype A than with B and vice versa for Naxs. Stimuli equidistant from the two prototypes (i.e., 4 features away) are not included. Stimuli are separated into two sets: training and generalization.

Training (20 mins - outside scanner): Total 240 trials are presented consisting of 8 stimuli items, presented 6 times for 5 blocks each with breaks. All training exemplars are two features away from each of the two prototypes (#6 and #2 in Fig. 6). Participants press one of two buttons to classify each item into Mip or Nax family, at their pace, with correct/incorrect feedback provided as green check/red X, respectively. Prototypes A/B are never shown.

Generalization (8 mins - in-scanner): Total 68 trials are presented consisting of 48 new stimuli items (not presented at training) comprised of 8 items which are each distance (1, 2, 3 features) away from prototype A and B, in addition to the two prototypes (#8 and #0 in Fig. 6) presented twice, and 8 training items presented twice. Items 4 features away, i.e., equidistant from the two prototypes were not included. Trials are presented broken into 2 blocks for classification as during training, but without feedback. Each trial comprises a fixation cross (4s) followed by the stimulus for 5s, a total of 9s which is needed to model individual trials for fMRI.

Model fitting: Prototype and exemplar model fits are estimated from trial-by-trial generalization data in each participant as in Dr. Zeithamova's studies (see (8) for computational details of modelling, described below conceptually). Dr. Zeithamova serves as consultant and has worked with Key personnel Dr. You on the analysis of the preliminary data.

Prototype models assume that categories are represented by their prototypes (i.e., the combination of typical category features from all training items in each category). The similarity of each novel exemplar presented during the Generalization phase to each prototype is computed, assuming that perceptual similarity is an exponential decay function of physical similarity (1, 2, and 3 features away) and taking into account potential differences in attention to individual features (121). Parameters are estimated from the pattern of behavioral responses, separately for each participant, taking into account attention weights for the eight stimulus features and sensitivity, the rate at which similarity declines with distance.

Exemplar models assume that categories are represented by their training exemplars, and test items are classified into the category with the highest summed similarity across category exemplars. Following (81, 122), similarity of an item to category A is computed taking into account the training items from category A, and the remaining parameters are as described above. For both models, the probability of assigning a stimulus x to category A is equal to the similarity to category A divided by the summed similarity to categories A and B. For each participants' generalization responses, the best fitting attention to each feature and sensitivity parameters are estimated, separately for each model. For each trial, the probability of the participant's response under the assumptions of each model is computed. For a given set of model parameters, there will be a specific probability value for each trial. These trial-by-trial model predictions are then compared with the participant's actual series of responses. For example, if the participant chose category A on a trial where the model predicted a 70% chance of picking category A, then there is an error of 30%. Model parameters are then tuned so that the model predictions are as close as possible to the observed pattern of responses. Specifically, an error metric (negative log likelihood of the whole sequence of responses) is computed for each model by summing the negative of log-transformed probabilities. This summed value is minimized by adjusting attention weights and sensitivity parameters using standard maximum likelihood methods, implemented using the "fminsearch" function in MATLAB (MATLAB 2018a, MathWorks). Parameters for each model and each participant are optimized separately. After optimization, prototype and exemplar model fits are used to generate neuroimaging regressors (see below) to identify regions tracking predictions of each model.

Identification of learning bias: Heterogeneity in learning bias is characterized by testing whether one model (prototype or exemplar) fits generalization performance reliably better than the other in each participant using Monte Carlo simulation. For each subject, a vector of random responses to the generalization trials is generated and to fit both prototype and exemplar models as described above. This procedure is repeated 10,000 times to generate a subject-specific null distribution of model fits for each

model, and then the observed prototype and exemplar model fits are compared to this null distribution to determine whether one or both models fit the participant's data better than chance. This is determined by comparing the actually observed model fit to the null distribution of fits and testing whether the observed model fit appears by chance with a frequency of <5% ($p < 0.05$, one-tailed). Model fits range from 0 (perfect fit, no error) to ~45 observed in our pilot data and (8) and are normally distributed; the upper limit depends on the number of trials as the error is summed trial-by-trial and the more trials, the larger the error. To determine whether one model fits reliably better than the other, the observed difference in model fits (fit exe - fit proto)/(fit exe + fit proto) is compared to the null distribution of differences in model fits generated by the simulation. One model is deemed a winner for the given participant when that difference score appears by chance with a frequency of <5% ($p < 0.05$, two-tailed)

**Characterization Measures:** Characterizations are related to inclusion and exclusion criteria for the study. These will be administered at baseline testing, and no measure will be adapted.

- **Wechsler Abbreviated Scale of Intelligence-2 (WASI-2):** The WASI is a characterization measure for this study used to help ensure that participants IQ's meet inclusion criteria. This measure will be administered by a member of the research team during a study appointment and will occur only at baseline. Please note, WASI-2 will only be done if the participant has not received an IQ test in the past two years. If they have, the scores of the prior IQ will be utilized.
- **Social Communication Questionnaire (SCQ):** The SCQ will be used as a characterization measure to determine autism symptomatology. This parent-report questionnaire will be administered at baseline only to assist in determining study eligibility.
- **Autism Diagnostic Observation Schedule (ADOS-2):** The ADOS will be used in order to confirm autism diagnoses for specific participants that do not meet inclusion criteria based on the SCQ. This measure will be administered by a trained clinician on the study team and will only occur at baseline for those participants who require it. If a participant has received a prior ADOS, the results of that evaluation will be reviewed by study staff to determine if participant meets criteria or if further evaluation is necessary.
- **Social Responsiveness Scale (SRS-2):** The SRS-2 will be used as a characterization measure to determine the severity of autism spectrum disorder symptomatology. This is a parent-report questionnaire that will be completed at all three time points and will serve as a covariate in our analyses.

**Other Covariates of Interest:** We assess parent-report of ASD severity through the Social Responsiveness Scale (Constantino & Gruber, 2012) as a covariate in our analyses. We also will ask parents and participants to complete other cognitive assessments and questionnaires.

## Section 4: Study Design

### Aims 1 & 2: Intervention Effectiveness

**Study Design:** This is a single-center Phase 2 clinical trial. This study uses a sequential case-controlled, clinical trial design. To increase power and internal validity, at each wave, participants will serve as their own control. Participant's age will be taken into account when forming the groups to ensure group cohesion.

**Number of Study Groups & Description of Interventions:**
Each participant will serve as their own control and will be evaluated (behavioral, cognitive, and neural response) at 3 time points at 8 month intervals (baseline-T1, pre-UOT-T2, post-UOT-T3). An additional follow-up time point (T4) will occur 8 months after T3 and will just consist of online questionnaires. Use of 2 baseline time points (T1, T2) spaced equally with pre- and post- assessment time points (T2, T3) provides a developmental control against which to assess response to treatment. See Timeline, Measures (Table 2), and Imaging procedures below. Three time points of assessment and intervention will be conducted with 18 participants in each wave. 8 months after baseline assessment, the pre-UOT-T2 assessment will occur and each participant will be enrolled in an 8 month long UOT group, meeting weekly in the CNH Center for ASD. The third assessment will occur after the completion of the UOT

group-T3. Senior research staff (clinical psychologists) will conduct therapy groups with 8-10 participants each. Two parent trainings will be delivered by study staff to support generalization of skills. Trainings focus on principles of EF and ASD, lesson content, and how to teach and model self-regulatory scripts.

**Specialized Study Team Training:**

- **EFCT:** We will train administrators to 85% reliability with a master coder through video recordings. Administrators must achieve 85% for three consecutive administrations to be considered reliable.

## Section 5: Study Enrollment and Withdrawal

### 5.1 Study Population, Recruitment and Retention

**A total of approximately 54 youth will participate in the study (age range 14-18). These participants will be evaluated at multiple timepoints before and after receiving UOT:HS. We anticipate having to screen up to 75 participants to accommodate ineligibility. All participants will be enrolled by CNH and GU.**

### 5.2 Inclusion Criteria

All participants must be:

(1) 14-18 years of age inclusive. (Age range selected to maximize scanning success, but could be expanded in future trials to cover full age range for which UOT is effective.)

(2) full scale IQ ≥ 80 on a standardized IQ test, either confirmed through educational or clinical testing within the last two years **or** confirmed by the WASI-2 administered by research personnel. *If current IQ testing (FSIQ) is not interpretable based on discrepancies between verbal and perceptual skills, we will use the best available verbal IQ estimate.*

(3) Broad ASD diagnosis according to DSM-5 criteria established by one of the following:

(a) Parent report of prior clinical diagnosis of ASD OR school service eligibility of autism confirmed by meeting cutoff criteria on the Social Communication Questionnaire (i.e., raw score ≥ 11) or the Autism Diagnostic Observation Schedule-2 (ADOS-2), Module 4 (total score ≥7). If an ADOS-2 is required, a child clinical psychologist with specialized training in autism and neurodevelopmental disorders, utilizing informant report measures and results of the ADOS-2, will determine final diagnosis. If an ADOS has been previously completed, the clinical psychologist reviewing the case will review the report to determine diagnostic eligibility, following the DSM-5 criteria for ASD.

(b) Parent report of ASD symptoms with review of intake materials supporting evidence of an autism diagnosis and confirmed by an abbreviated research diagnostic evaluation. This will consist of completion of the Social Communication Questionnaire and the ADOS-2, both of which will be reviewed by a child clinical psychologist, as well as any previous medical or school report. The clinical psychologist reviewing the case will use the available information to determine diagnostic eligibility, following the DSM-5 criteria for ASD.

(4) Intact or corrected hearing and vision.

(5) Parents/guardians speak and read English with sufficient fluency for completion of consent forms and informant questionnaires; youth participants will use/understand English as a primary or secondary language with sufficient fluency to engage effectively in UOT group therapy conducted in English, and for valid administration of neuropsychological and behavioral measures.

(6) Appropriateness for group therapy treatment, as determined by the clinical portion of the study team

### 5.3 Exclusion Criteria

1) Presence of any condition (based on medical history by parent report) that would interfere with the participant's ability to participate in the study or the intervention.
(2) To preserve the integrity of the neuroimaging data, participants will be excluded if they have a history of neurological disorder (other than ASD or ADHD), such as an established epilepsy diagnosis, significant brain trauma, hydrocephalus, CNS infection, or stroke.
(3) Contraindications for MRI such as metal implants, dental braces, pregnancy (determined by parent or self-report).

## 5.4 Vulnerable Subjects

This proposal involves children, a vulnerable subject population. All HHS Subpart D—Additional Protections for Children requirements will be followed. As stipulated in 46.403, the protocol (including requirements for assent and consent) will be certified through CNH and GU IRBs prior to any study activities taking place. Research staff will be certified by the CNH and GU IRB to conduct research on human on subjects, especially as related to children. This study is categorized as 46.404, research not involving greater than minimal risk, and we will follow 46.408 requirements for permission by parents or legally authorized representatives and for assent by children. Throughout the project, study staff will continue to work with the IRB to protect the rights and confidentiality of all individuals who participate in data collection. There is limited possibility in this study that participants will experience any untoward effect. Nonetheless, we will monitor closely the acceptability of the procedures and seek to understand any concerns from parents, participants, or school staff in order to address them quickly. If a formal concern were to be voiced by a participant, it would be immediately addressed to the best of our ability and would be quickly reported to the IRB. We are hopeful that the serious attention we have paid to these issues will prevent such occurrence

## 5.5 Recruitment

Recruitment recapitulates a process that has been highly successful during our previous clinical trials and neuroimaging protocols. The Center for Autism Spectrum Disorders at Children's National, directed by Dr. Kenworthy (PD), has: a large participant pool of 2,400 individuals with ASD, existing mechanisms for recruitment of new participants through clinic and community referrals; and a history of successfully meeting recruitment targets for intervention and imaging protocols. Participants will also be recruited through social media posts and advertisements on approved social media pages, flyers at local providers, and referrals through the Children's National clinics. IRB approval will be obtained from CNH and GU. Study staff will screen families and invite them for a baseline/eligibility appointment. Please note that no PHI will be recorded prior to study enrollment and we will not be accessing any medical records to determine study eligibility.

Potential eligible participants will be contacted by a member of the research team and study procedures will be explained. Before participating, parents and youth will need to read and sign a consent/assent form and HIPAA waiver, prepared by the PDs and approved by the IRBs at CNH and GU. A member of the study team will also explain the purposes, benefits, and risks of the project to the subjects, and offer an opportunity to ask questions and/or decline participation. A full description of the nature of the study, the requirements of their participation in it, and the risks and benefits of the study will be explained to potential participants by the PDs, study staff, or a trained research assistant.

All participants will be volunteers. Any eligible family will be offered the opportunity of participating in this study. All HHS Subpart D—Additional Protections for Children will be followed. Every participating child will have informed consent from one of their parents or legally authorized representatives. Documentation of child assent will also be obtained. Participants 18 years old at enrollment will be asked specific structured questions after the consenting process, but before consenting, to ensure they have sufficient understanding to consent to the study (e.g., "What are some of things you will be asked to do in this study?" "Whose decision is it to be in the study?" "How would you tell us if you wanted to stop being in this study?" "What are the risks of this study?" "Will being in this study affect your care at CNH?"). If it is determined that these participants are not capable of providing consent, they will be excluded from the study. Participants may withdraw from the study at any time. Participants will be reimbursed according to

the guidelines for normal volunteer research as approved by the IRB. All activities, procedures, and written information will be approved by the IRBs at CNH and GU.

## 5.6 Retention

Study staff have extensive prior experience in recruitment and retention of participants for studies with multiple data collection points, including longitudinal studies and pragmatic community intervention studies. In order to maximize our ability to retain participants for all three timepoints, we will employ the successful strategies from our prior clinical trials for which we have had generally low attrition rates (1.3-5%).

Efforts will be made to establish relationships with the individuals enrolled in the study via contact with the research faculty and staff, including the project directors, co-investigators, and research staff. These include:

- Complete a review of patient facing procedures with Center for ASD Parent Advisory Board prior to initiation of the study and revision of procedures as needed.
- Full disclosure of assessment procedures prior to enrollment, including exploration of plans for orthodontic work or other impediments to participation in an fMRI study.
- At the first appointment, research staff will gather contact information from families, include home address, email address(es), and multiple phone numbers. Study staff will confirm contact information at each appointment, thereafter.
- Throughout the 8-month waiting period families will be provided with supports and resources to maintain study engagement.
- Study staff will document the primary mode of preferred communication at each appointment. Previous studies have been successful in using a wide variety of modes of communication, including the use of dedicated study staff mobile phones for text communication with families.
- Study staff will set appointments for the next assessment period at the end of each assessment appointment. Study staff will note in the participant file the 4-week range (2 weeks before and 2 weeks after target visit date) within which follow-up appointments may take place (i.e., the visit window period) so this window is clear when speaking to participants regarding requests to reschedule missed or future visits,
- Study staff will create calendar prompts or automatically-generated emails that alert study staff or participants of upcoming study visits one week prior to the start of the visit window period.
- Families will receive increasing compensation for participation across appointments to defray costs associated with time and travel ($30 at Time 1, $45 at Time 2, and $60 at Time 3, in addition to $50 for completing MRI scanning and parking while at Georgetown; $15 at T4 will cover completion of online questionnaires).
- Families will also receive postcards from study staff thanking them for their participation. Families will be able to “opt-in” to an electronic newsletter describing study progress and providing (non-intervention related) resources for autism or autism-friendly events in the area.
- All participating families will have the option of requesting a report detailing the results of the testing after visit 1. Additionally, families will be able to request a report after completing the intervention. This reduces potential reporting bias based on knowledge of testing results for prior appointments.

## 5.7 End of Participation Criteria and Procedures

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate a participant’s study involvement if:

- Any adverse event (AE), or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The participant has completed the intervention, if applicable, and all baseline, endpoint, and follow-up assessments are completed.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination will be provided by the suspending or terminating party to participants, site investigators, the funding agency and regulatory authorities (e.g. OHRP). Given the low-risk nature of this study, this is an unlikely possibility. However, If the study is prematurely terminated or suspended, the PD will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant study termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient study team or site participant compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility
- Loss of study funding

The study may resume once any concerns about safety, protocol compliance, data quality or funding are addressed and satisfy the sponsor, IRB and OHRP.

## Section 6: Study Procedures

### 6.1 Informed Consent/Assent and HIPAA Authorization

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study. It continues throughout the individual's study participation. Consent and assent forms will be IRB-approved. The consenting process will take place virtually utilizing REDcap e-consent procedures prior to timepoint one.

**Virtual Consent Procedures:** At the time of enrollment, a subject or their parent(s)/LAR is given a unique internet link which opens the consent form in REDCap. The investigator or designated member of the study team reviews each page of the consent with the subject or LAR via telephone or Zoom Telehealth. When the study has been fully explained and the subject's questions have all been answered, the subject moves to the electronic signature page in REDCap and indicates their consent by typing their full name in the space provided on the electronic form. There is also a signature page for the person who obtains consent from the subject. The complete consent form, including the electronic signature page, is maintained in REDCap as a PDF document. This can be printed and sent to the subject by U.S. mail when appropriate or provided to them at their next in-person appointment.

Once informed consent and/or assent has been obtained, the study staff will have the form reviewed by a study team member, who will confirm that it is fully completed before it is stored in the secure database.

Some participants may turn 18 during the course of their involvement of the project, so we will consent them as adults at the next study visit following their birthday.

### 6.2 Screening Process

After expressing interest in the study participants will be screened by a member of the study team over the phone or via Zoom Telehealth. Screening questions will be asked to the include questions to rule out exclusionary criteria and confirm inclusion criteria. Additional questions may be asked to determine clinical utility and concerns related to participation in the UOT intervention.

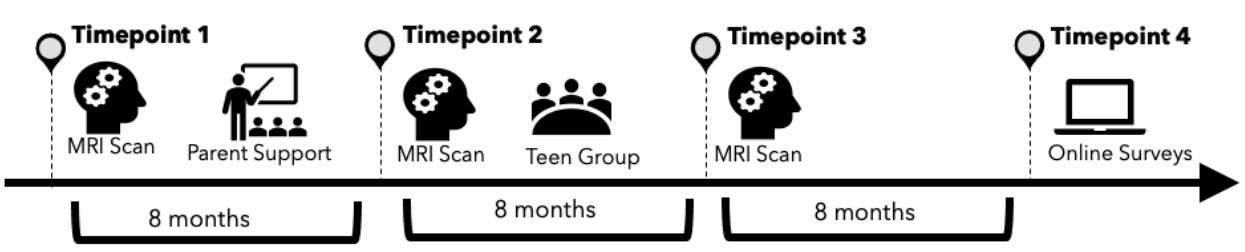
After the screening, parents will be given the option of completing the Social Communication Questionnaire (SCQ) over the phone, Zoom Telehealth, or online via a REDCap survey. This is to determine whether an ADOS will need to be administered at the baseline session. If participants ultimately decide not to join the study, this data will be destroyed. If they decide to join the study, answers on the SCQ will be entered into the study database. If a participant remains eligible after screening, a baseline assessment will be scheduled where IQ testing and diagnostic testing, if necessary based on

their answers on the SCQ and any available report review, will occur to confirm they meet all inclusion criteria prior to beginning the intervention. Participants that have received an IQ assessment in the last two years will not need to repeat IQ testing. Participants will only be excluded after the baseline assessment if they then do not meet inclusion criteria.

Prior to starting UOT group, all participants will complete a suicide and risk assessment. Families may also be asked to complete additional questions that all families complete when receiving services at the Center for Autism Spectrum Disorders at Children's National.

## 6.3 Study Interventions and Follow-Up

1. **Timepoint 1:** Participants will be asked to go to Georgetown University or a Children's National location for behavioral assessments. All imagining will occur at Georgetown. They will complete scanning procedures, characterization and eligibility measures, and behavioral assessments.
2. **Waiting Period:** There will be an 8-month waiting period before the intervention. During this time, there will be optional parent sessions with experts. Resources will be provided on the transition to adulthood.
3. **Timepoint 2**: Following this waiting period, participants will be asked to repeat the MRI scanning and behavioral assessments.
4. **Intervention**: Following the second study appointment the *Unstuck and On Target: High School* treatment program will begin. This program will last approximately 8 months and take place at a Children's National location. The treatment program is made up of approximately 25 hour long sessions that take place weekly and will be implemented by a trained psychologist.
5. **Timepoint 3**: At the completion of the entire treatment program, we will ask participants to complete the MRI scanning and behavioral assessments again.
6. **Timepoint 4**: Participants will be asked to complete a few online questionnaires about 8 months after visit 3.




## 6.4 Description of Study Procedures/Evaluations

*Unstuck and On Target: High School (UOT:HS) Intervention:* The UOT:HS group curriculum targets flexibility and planning skills using CBT techniques across 25, 1-hour lessons delivered by trained clinicians. UOT:HS contains four units, each targeting pivotal transition-related skills that address the specific EF challenges faced by young adults with ASD. The first unit teaches neurodiversity & self-advocacy, so teens can learn to accept and appreciate their learning differences, and in turn, advocate for help when needed to reach their goals. The second unit targets tools for efficient planning: understanding short- and long term- goals, creating individualized time-management routines to stay focused on goals, and coping with stress that can derail the planning process and progress. The third unit builds skills needed to reach teen's personal goals: staying motivated, creating individualized reminder strategies, and using reputation building and compromise strategies when teens need another person's help to reach their goal. Unit four guides teens in creating individualized plans for their goals (Plan A), anticipating planning obstacles, and flexibly problem solving obstacles in an iterative manner (Plan B). The final unit practices group planning strategies in the context of celebrating teen's efforts. With permission from all group members, several of these sessions will be video or audio recorded in order to code for key intervention ingredients. If someone in the group does not want to be recoded then we will not record the group at all.

*Behavioral Sessions:* Eligible participants will complete three behavioral sessions, one prior to the waiting period, one before the intervention begins, and one after the intervention. Sessions may be split to accommodate participants needs. During the behavioral session, participants will be asked to perform various computerized and paper-and-pencil assessments and tests. These may include The Wechsler Abbreviated Scale of Intelligence (WASI-2), the Executive Function Challenge Task, as well as other cognitive assessments. Parents will also be asked to complete a demographic questionnaire, The Social Communication Questionnaire (SCQ), The Social Responsiveness Scale (SRS-2), the Adaptive Behavior Assessment System (ABAS), as well as other questionnaires about their child's behaviors. The assessments and tests above are standardized instruments used in clinical psychological/psychiatric practice. While some of the individual measures may change, the general constructs of IQ, executive functioning, adaptive behaviors, and autism symptoms will be assessed during these sessions.

*MRI Scanning*: Imaging will be performed with a 3T MRI Siemens Magnetom Prisma located at the Center for Functional and Molecular Imaging (CFMI) at GUMC. An imaging technician positions participants in the scanner, in the supine position with a 64 channel head coil. Custom designed Styrofoam head molds (https://caseforge.co/) will be used to minimize motion (123), in addition to the use of the "mock scanner" to increase compliance; TV/video during structural MRI reduces motion. CFMI staff or a parent may remain in the MRI suite with each child to ensure high quality and consistency of scans. Stimuli are back projected (using E-Prime) with responses collected via fiber-optic button boxes.

Structural MRI (8 mins) A standard high-resolution T1-weighted MPRAGE anatomical sagittal image with parameters:TR = 1900 ms; TE = 2.52 ms; TI = 900 ms; flip angle = 9°; matrix size = 256 × 256; 176 contiguous slices; FOV = 256 mm; slice thickness = 1 mm; voxel size = 1.0 × 1.0 × 1.0 mm; generalized autocalibrating partially parallel acquisitions (GRAPPA) factor = 2. These images are used to determine spatial normalization parameters for normalization of functional images to standard stereotaxic space.

Functional MRI (15 mins) A field map scan followed by 3 functional runs will be acquired, including a resting state run for 6 mins, followed by two A/B category task generalization runs, each lasting 4 mins (Training will be completed outside the scanner immediately before), using a multiband gradient echo pulse sequence with parameters: TR=2000ms; TE=29 ms; flip angle=90°; matrix size=100×100; FOV=208 mm; voxel size=2.0×2.0×1.8 mm; multiband (MB) factor slice acceleration PE= 2); 72 contiguous slices oriented 15° off the AC-PC line to align to the long axis of the hippocampus. The first 4 TRs will be discarded to allow for signal stabilization and excluded from analysis.

Pilot data shows that teens are able to complete these tasks successfully inside of the scanner. During screening research staff will gauge each participants ability to be inside of the scanner and any participants who clearly will not be able to do the scan will be screened out. Eligible families will be provided with a social story outlining the scanning visit as well as video clips of the types of noises teens should expect. If at the time of scanning participants are not comfortable completing tasks inside of the MRI scanner they can complete them on a computer.

Each behavioral/MRI scanning session will take between 2-3 hours. If in-person contact is restricted, the majority of the baseline assessments will be shifted to a virtual format with any procedures that need to be conducted in person (such as the MRI scan) completed with appropriate PPE and following CDC guidelines on physical distancing. Additionally, administration of ADOS, if necessary, can be done at a future appointment time.

*Online Questionnaires:* Participants and their parents will be asked to complete online questionnaires approximately 8 months after the last in person MRI scanning and behavioral assessment visit. These questionnaires are to look at the long term impact of UOT:HS and should take no more than 2 hours.

### 6.5 Study Team Training and Intervention Reliability

- Before the trial starts, Drs. Kenworthy, Vaidya, Pugliese, and Verbalis, will meet bi-weekly to finalize recruitment strategy, study protocols, clinical trial design, review training procedures, and review data collection procedures. Our ongoing communication plan includes an intensive teleconference schedule

during key phases in the study (start-up phase, month prior to baseline, endpoint, and follow-up appointments) and a regular schedule of meetings throughout to evaluate study progress, review safety/compliance issues, and resolve any emergent study-related issues.
- During each enrollment period, Drs. Kenworthy, Vaidya, Pugliese, and Verbalis will meet bi-weekly with research coordinators/postdoctoral fellow to review any issues or problems and ensure recruitment practices conform with IRB standards
- Throughout the course of the study Drs. Kenworthy, Vaidya, Pugliese & Verbalis will conduct weekly meetings with research coordinators and the postdoctoral fellow to identify weekly goals and ensure milestones during that periods are met in an efficient and timely manner. These meetings will be used to conduct all necessary training required to complete study objectives (e.g., review consenting practices during recruitment). Quarterly meetings will review HIPAA compliance, and protection of human subjects information. Drs. Kenworthy, Vaidya, Pugliese & Verbalis will meet bi-monthly to resolve any problems with the research coordinator team, review the budget, and plan for upcoming expenses.

### 6.6 Concomitant Interventions and Procedures

We place no restrictions on medications, treatments, therapies, or procedures that participants may undergo while enrolled in this research study. We will collect data on these items for characterization purposes and to use as covariates in our analyses.

## Section 7: Safety Assessments and Reporting

### 7.1 Adverse Events (AEs)

**Definition:** According to CNH IRB, an adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:
- Results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significance

**Severity Grading**: AEs will be assessed by trained research personnel overseen by Drs. Kenworthy & Vaidya. We use the following grading system outlined by CNH IRB:
- Mild: Event requires minimal or no treatment and does not interfere with daily activities.
- Moderate: Event results in low level of inconvenience or concern with the therapeutic measures. Moderate events may interfere with functioning or study conduct.
- Severe: Event interrupts participant's daily activities and may require systemic treatment. Severe events are usually potentially life-threatening or incapacitating.

**Expectedness:** An event is considered "unexpected" if it is not a known risk of the research intervention(s) or if it does not routinely occur in the subject population at the frequency or intensity seen during the study.

**Relationship to Intervention:** Assessment of relationship of the event to the study intervention will be determined on a scale of relatedness as follows:
- Probable: AE is likely to be related to the study
- Possible: AE may be related to study
- Unlikely: AE is doubtfully related to the study
- Not Related: AE is clearly not related to the study.

### 7.2 Serious Adverse Events (SAEs)

**Definition:** According to CNH IRB, a serious adverse event (SAE) is an AE that is one or more of the following:

- Fatal
- Life threatening
- Requires or prolongs a hospital stay
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Another important medical event (e.g., those that may not be immediately life threatening, but may jeopardize the subject, and/or require intervention to prevent one of the outcomes noted above)

## 7.3 Unanticipated Problems (Ups)

**Definition:** The CNH IRB considers unanticipated problems involving risks to participants or others to include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given the research procedures described in the study documents (e.g., consent, protocol) the participant population; AND
- Related or possibly related to participation in the research. "Possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; AND
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

**AE/SAE/UP Documentation Procedures – Case Report Form:** At each study appointment, the study team will ask the participant/LAR if any AE/SAE/Ups have occurred since the last study contact. All adverse events will be captured on the adverse events CRF. The case report form directs the clinician to make a judgment about whether the AE can be attributed to the study intervention. Information collected includes event term, onset date, severity, relationship to study intervention (assessed and documented by an authorized study team member), and date of event resolution/stabilization. All events occurring during the study period, starting with the visit 1 appointment and for 30 days after the visit 3 (after completion of the intervention) appointment must be documented, regardless of relationship to the research intervention. All events which meet the definition of a serious adverse event or unanticipated problem that occur within that study period will be followed until resolved or stable.

- Any medical condition that is present before the visit 1 appointment will be considered a baseline condition; it will not be reported as an AE. However, if the participant's condition deteriorates during the study, the worsening of the condition will be recorded as an AE.
- Changes in the severity of an AE will be documented to allow assessment of the duration of the event at each level of severity. AEs characterized as intermittent will require documentation of onset and duration of each episode.
- We will continue to monitor participant responses related to suicidal thoughts. If endorsed we will adhere to the urgent needs protocol described above, and determine its relationship with the intervention, and follow the procedures stated above.

**Remediation of UPs involving risks to subjects or other**: We will consider the following remediations as appropriate to the situation:

- Changes to the research protocol
- Modification or inclusion/exclusion criteria to mitigate newly identified risks
- Implementation of additional procedures for monitoring subjects
- Suspension of enrollment of new subjects
- Suspension of research procedures in currently enrolled subjects
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled subjects.

**Serious Adverse Event and Unexpected Problem Reporting:** This is a low-risk phase 2 clinical trial. Adverse events are not expected in this behavioral trial. All suspected adverse reactions to study

interventions that are both serious AND unexpected will be reported to the CNH IRB. According to the NIH Reportable Events Policy, if there is a reportable event, the PD will notify the IRB and submit the following in writing to the NIH Program Official (PO) and: identifying information for the research protocol (e.g., title, investigator's name, and the grant/contract number); the date on which the event occurred and the date at which the PD became aware of the event; a detailed description of the event and impact on the participant(s); a detailed description of the measures taken (including clinical) in response to the event (if any); Confirmation that the appropriate monitoring entities and regulatory bodies have been notified as needed; and a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the event.

| **Reportable Event** | **When is Event Reported CNH IRB** | **When is Event Reported to the NIH** | **Reported By** |
|---|---|---|---|
| IRB/ISM/OHRP/ Suspensions or Terminations | | Any suspension or termination of approval must include a statement of the reason(s) for the action and must be reported promptly to the NIH PO within **3 business days of receipt.** | IRB/Dr. Kenworthy & Dr. Vaidya |
| Deaths related to study participation | Unexpected death that is related or possibly related to the research must be reported within **1 business day** of learning of the event. A follow-up report must be submitted within **2 business days**. | Deaths must be reported immediately (no later than within **5 business days)** of the principal investigator first learning of the death. | Dr. Kenworthy & Dr. Vaidya |
| Unexpected Serious Adverse Events Related to Study Participation | Reported to CNH IRB within **5 business days** of notification of the event. | Reported to the NIH PO within **10 business days** of the study team becoming aware of the SAE. | Dr. Kenworthy & Dr. Vaidya |
| Unanticipated Problems:<br>• Data breach/HIPAA violation (loss, theft, or other unauthorized disclosure of private information such as PHI or confidential data)<br>• Internal unexpected SAEs<br>• Loss or theft of research equipment, incentives, or other study materials<br>• Child subject is transferred from his or her parents/guardians to foster care (child becomes a ward of the state)<br>• Serious complaint by a subject or family member<br>• Enforcement action such as an unfavorable audit report | • Data breaches and HIPAA violations will be reported within **1 business day** of learning of the event.<br>• All other Ups will be reported within **7 business days**. | Reported to the NIH PO within **10 business days** of the investigator learning of the event. | Dr. Kenworthy & Dr. Vaidya |
| Serious or Continuing Noncompliance<br>• IRB approval expired | Failures to follow federal, state, or local regulations | Reported to the NIH PO within **10 business** | CNH |

| | | | |
|---|---|---|---|
| • Research activities (including follow-up and data analysis) continued after IRB approval expired<br>• Research activities were conducted without prior IRB approval<br>• Subjects were not recruited according to the IRB-approved plan<br>• Use of unapproved recruitment methods or materials<br>• Informed consent and/or assent was not obtained or was obtained improperly<br>• Invalid consent/parental permission and/or assent form was used (e.g., expired, no IRB stamp)<br>• Changes were made to informed consent and/or assent documents without IRB approval<br>• Coercion or undue influence of study subjects to obtain their agreement to participate<br>• PHI was collected and recorded without IRB approval<br>• Scope/intent of the study was changed without IRB approval<br>• Study staff conducted research activities without appropriate qualifications/training<br>• Study staff did not receive adequate supervision<br>• Subjects placed at risk due to no or inadequate monitoring of the data<br>• Missing or no source documentation | governing human research, institutional policies and procedures, or IRB requirements or determinations within **7 business days**. | **days** of IRB determination | |
| Adverse Events that are expected & unrelated to the study | Routine, expected adverse events will not be reported to the CNH IRB. | For all AEs and SAEs that are deemed expected and/or unrelated to the study, a summary will be submitted to the NIH PO with the **annual progress report** | Dr. Kenworthy & Dr. Vaidya |
| Protocol Deviations:<br>• Enrollment of ineligible subject(s)<br>• Enrollment of more subjects than approved by the IRB<br>• Additional study procedure(s) conducted without IRB approval<br>• Study procedure(s) omitted | Events that depart from the IRB-approved study protocol will be reported to CNH IRB within **7 days**. | With the **annual progress report** | Dr. Kenworthy & Dr. Vaidya |

| | | | |
|---|---|---|---|
| • Subject assessment outside window<br>• Improper storage of study device(s) | | | |

- If any needed information is missing or unknown at the time of initial reporting, the study team will actively try to obtain it. The study team will maintain records of efforts to obtain additional follow-up information. Any additional relevant information to a previously submitted report will be submitted to oversight bodies as soon as the information is available.
- All SAEs and UPs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or stable. Other supporting documentation of the event may be requested by oversight bodies and should be provided as soon as possible.

### 7.4 Study Halting Rules

As a non-invasive behavioral intervention, we do not anticipate any safety issues that would result in halting the study.

## Section 8: Statistical Considerations and Analysis

### 8.1 Statistical and Analytical Plans (SAP)

The formal SAP will be reviewed and finalized prior to the start of data collection. Please see below sections for proposed analytical plans.

### 8.2 Statistical Hypotheses

AIM 1, H1: At both T1 and T2, stronger prototype bias (higher prototype than exemplar model fit) and greater vmPFC activation will be associated with better flexibility and adaptive behavior; H2: T1 versus T2 comparison will test the stability of learning bias.

AIM 2, H1: Following UOT (T3), ASD youth will exhibit stronger prototype model fit, flexibility (EFCT Flex, BRIEF Shift) and adaptive behavior (ABAS General Adaptive) relative to T2, and prototype learning at T2 will predict treatment response. H2: mPFC activation will be positively associated with UOT behavioral response.

Aim 3. H1: vmPFC-MTL resting state FC and MTL network FC will be associated with prototype learning and H2: FC will mediate the association between prototype learning change and behavioral improvement following UOT

### 8.3 Description of Statistical Methods

**AIM 1 – Hypothesis 1:** Behaviorally, the observed difference in model fits (fit exem - fit proto)/(fit exem + fit proto) will correlate with EFCT Flexibility, BRIEF Shift, and ABAS GAC scores, such that stronger prototype learning will relate to better flexibility and adaptive behavior. We expect this result at T1 and T2. Similar correlation analysis will be conducted with vmPFC and MTL beta values from the prototype and exemplar regressor, respectively. We expect vmPFC, but not MTL, to correlate with better flexibility and adaptive behavior.

**AIM 1 – Hypothesis 2:** We expect stability of learning mechanism such that prototype and exemplar model fits will correlate between T1 and T2; those with statistically significant learning bias at T1 will also show the same at T2.

**Aim 2 – Hypothesis 1**: In this self-controlled study, and for each outcome, our primary analyses will use an analysis of variance (ANOVA) comparing the scores (EFCT Flexibility, BRIEF Shift, ABAS GAC) at all three time points. The main contrast of interest will be to compare the scores before (T2) to those after (T3)

the intervention covarying for T2 pre-intervention values. In addition, we are interested in the difference of difference contrast (T3-T2) – (T2-T1) to evaluate whether the change observed pre to post intervention is higher than change during the baseline period. We will report p-values from paired t-tests as well as 95% confidence intervals for each contrast and each outcome. We will control for multiple testing using a Benjamini-Hochberg multiple testing strategy (126). If some subjects have influential or outlier values in one of these outcome (outlier below or above 1.5*Interquartile range), we will use bootstrap to derive the p-values and 95% confidence interval. Reliability of UOT-induced change in learning bias will be assessed by using model fit values at T1 and T2 to generate test-retest distribution of *mean* and standard deviation (SD) (T2-T1) from the 54 participants. We will then calculate the reliable change index for T3 by deriving the Z score for each subject: *subject*(T3-T2) minus *sample* mean(T2-T1) divided by *sample* SD(T2-T1). Responders will be categorized as Z>1.5. We also expect individual variation in prototype model fit change (T3-T2) to correlate with UOT behavioral response (T3-T2) on EFCT Flexibility, BRIEF Shift, and ABAS Composite scores such that those with a stronger prototype fits post-UOT will have more improvement in flexibility and adaptive function.

**Aim 2 – Hypothesis 2**: We expect that vmPFC activation from the prototype regressor will be higher in responders relative to non-responders (t-test). We expect T3-T2 vmPFC activation difference to correlate positively with improvement in flexibility and adaptive function.

**Aim 3 – Hypothesis 1:** vmPFC-MTL FC values and mean FC of the MTL network will correlate positively with learning model fit difference (stronger prototype learning) at T1 and T2.

**Aim 3 – Hypothesis 2**: We will test mediation of the association between T3-T2 prototype learning change and flexibility (EFCT Flexibility, BRIEF Shift) and adaptive (ABAS GAC) change (direct effect) by FC with a regression model; adding the FC values will reduce the significance of the direct effect, thus, showing that connectivity is a partial mediator. We expect the MTL network FC to be a stronger mediator than vmPFC-MTL, suggesting that UOT modulates a large-scale network dedicated to memory integration.

### 8.5 Sample Size

**Power analysis** was based on correlations with flexibility in Preliminary data, which ranged from .6 - .4 – using the lower *r=.4,* for 80% power and p=.05, N=45 is needed; factoring in 20% data loss to head motion estimated from our pediatric work, requires 9 additional participants; therefore our N=54 should be sufficiently sensitive to heterogeneity in flexibility behavior. Power for learning outcome cannot be calculated because there are no data for within-subjects comparison of learning parameters in past work to estimate effect size. Trial and imaging parameters of the category learning task are identical to that in Dr. Ziethamova's published studies, and thus, well-powered to reveal predicted activation in individual subjects. Regarding behavioral data. power analyses for the statistical models were conducted using Power Analysis and Sample Size Software (ncss.com/software/pass). We expect a moderate to high impact of our intervention on our endpoint with effect size (Cohen's d > 0.6). Our preliminary UOT data found effect sizes of (0.68 to 1) based on paired sample t-tests. A sample size of 54 with 10% attrition rate will have >85% power to detect a moderate impact and type 1 error of 5% (2-sided).

## Section 9: Data Quality and Oversight

### 9.1 Study Team Quality Assurance and Quality Control

Data collection is the responsibility of the PIs with assistance from study staff. The PIs will be responsible for ensuring the accuracy, legibility, timeliness and completeness of the data reported. Only Institutional Review Board (IRB) approved research team members who have current HIPAA and Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) and human subjects protection training will be authorized to have access to research records.

### 9.2 Data Safety and Monitoring Plan

We have developed a data safety and monitoring plan that is appropriate for this study. Due to the low-risk nature of this study a monitoring board will not be created unless instructed to do so by the NIH. This plan

involves obtaining informed consent from parents and assent from all participants under the age of 18 and insuring confidentiality of research data for all participants. The informed consent will include discussion of possible risks and benefits inherent in study participation. This plan also includes the procedures described above to ensure safe storage of data and restrict unauthorized access to identifiable patient data, including password protection of any electronic file with identifiable patient information and maintenance of locked files for any hard copies of identifiable information. In addition, this plan includes procedures described below for responding to any adverse reactions to the treatments offered or revelation of a safety concern during the study.

**Risks in this study are considered minimal, with no adverse effects reported in the in-clinic and school-based pilots of the proposed treatment.** There will be a core monitoring team of licensed clinical psychologists that will serve as the oversight for this project to monitor the study and ensure the safety of the participants who will work in collaboration with the CNH and GU Institutional Review Boards (IRB). Safety and monitoring will be the responsibility of the Project Director at CNH (Dr. Kenworthy), Co-Investigator, Dr. Pugliese, and Project Coordinator at CNH (Dr. Verbalis). Drs. Pugliese, Dr. Verbalis and Dr. Vaidya will be actively involved in reviewing the progress of each participant and, in conjunction with Dr. Kenworthy, will report adverse events (AEs) and unexpected problems to the IRB.

Drs. Kenworthy, Pugliese, and/or Verbalis will meet bi-weekly with the research team to ensure participants safety and privacy. They will review any AEs and examine patterns across and within participants over time. Children constitute members of a vulnerable population and will thus be accorded special consideration. **This study is considered minimal risk, and there is limited possibility in this study that participants will experience any untoward effect.** Nonetheless, we will monitor closely the acceptability of the procedures and seek to understand any concerns from parents or participants in order to address them quickly. If a formal concern were to be voiced by a participant, it would be immediately addressed to the best of our ability and would be quickly reported to the IRB. We are hopeful that the serious attention we have paid to these issues will prevent such occurrences.

## Section 10: Ethical Considerations

### 10.1 Ethical Standard

The study team will ensure that this study is conducted in full conformity with the Regulations for the Protection of Human Subjects of Research codified in 45 Part 46 of the Code of Federal Regulations, Children's National and Georgetown University Policies and Procedures and Good Clinical Practices.

### 10.2 Institutional Review Board (IRB)

This project is under the IDDRC-DC umbrella and will be active at both CNH and GU, thus two IRB's will be informed of the study. The IRB at CNH will serve as the IRB of record. The IRB at CNH is comprised of individuals with sufficient expertise and diversity who review and evaluate ethical issues involved in research protocols. CNH currently has three IRB committees: two that review standard IRB protocol submissions and annual renewals, and one that examines clinically urgent situations, unanticipated funding issues, or unusual scientific circumstances that require a rapid IRB response. In 2011, we shifted from a paper-based system to a web-based system (Click Commerce), which has increased efficiency and ensured compliance. This was done at an institutional cost of almost $1 million. The Office for the Protection of Human Subjects (OPHS) is the administrative and regulatory compliance arm of the IRB process. Its function is to serve as the gatekeeper of all issues related to the protection of human research participants. OPHS acts as the liaison between the IRB committees and the research investigators, documents compliance with federal research regulations, and educates the CNH research community about the ethical conduct of research. Our IRB is AAHARP accredited. CNH has documented their Human Subjects compliance and the people involved are committed to the highest standards of ethical conduct of research with human participants.

The IRBs will be notified of study team updates via an amendment. Other study events (e.g., protocol deviations, data monitoring reports) will be submitted per the Children's National IRB Reportable Events Module.

## 10.3 Maintaining Subject Privacy

This study will take the appropriate measures to ensure the confidentiality and privacy of participants. If they meet initial inclusion criteria and remain interested, participants will be assigned a participant ID number to separate their data from PHI. All participants will be consented individually, either in a private testing room at a CNH location, Georgetown University, or virtually through Zoom Telehealth . During the consent process, we will offer verbal and written assurance of no negative consequences if participants decide not to participate & assurance that they can stop participating at any time. Signed consent forms will then be stored separately in a locked filing cabinet. We do not have access to the participants' medical records, nor do we require access to them.

## 10.4 Maintaining Study Data Confidentiality

Participants' data for the study will be stored with a unique alphanumeric identifier (no names or other identifying information) at CNH. All computers for this study will be password protected and located in locked private offices. All data will be scored on CNH computers that are password protected, and with software that require additional access codes. Data will be managed using REDCap (Research Electronic Data Capture, Harris et al., 2009) electronic data capture tools hosted at CNH. REDCap uses a secure web interface that utilizes web authentication, data logging, and Secure Sockets Layer (SSL) encryption. The software allows for data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance (e.g., audit trail, user-based privileges, secure sockets layer encryption, etc.). Access to the study's data in REDCap will be restricted to the members of the study team by username and password. Data will be de-identified when exported for analysis. Any paper records (e.g., semi-structured and cognitive interview forms, etc.) will be identified with the subject's assigned participant ID and will be maintained in a secure, locked cabinet in a private office. It will be stored separately from any documents or tables that contain participants' identifying information (e.g., names, student or patient IDs, addresses, phone numbers), including the informed consent forms.

Paper Data: Subject information from this study will be kept strictly confidential. All hard copies will be stored at the Center for Autism Spectrum Disorders in two separate filing cabinets. The first locked filing cabinet will store participant consent/assent forms and any release of information forms. In the second locked filing cabinet, we will store all hard copies of subject data and standardized study forms. Access to each cabinet will only be available to the study staff dedicated to the study and identified on this protocol. Identifiers will only be kept as far as the study remains open and is under IRB oversight. Once the study is complete and IRB oversight is finished, all identifiers will be destroyed.

Electronic Data: Data will be entered on a password-protected CNH computer, and managed using REDCap (Research Electronic Data Capture, Harris et al., 2009) electronic data capture tools hosted at CNH. REDCap uses a secure web interface that utilizes web authentication, data logging, and Secure Sockets Layer (SSL) encryption. The software allows for data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance (e.g., audit trail, user- based privileges, secure sockets layer encryption, etc.). Access to the study's data in REDCap will be restricted to the members of the study team by username and password. Data will be de-identified when exported for analysis. While all CASD staff have access to these computers, only members of the research team can view and log in to this database. Video recordings of measures administered during the testing battery will be used for teaching and training purposes throughout the duration of this study. Specific identifiers will be limited to participants' first names and full body image. Participants and parents may decline consent for audio/video recording for teaching and training purposes at any time and still participate in the study. If the participants and parents give consent for audio/video recording for teaching and training purposes, the audio/video records will be immediately removed from the recording device and stored in a secure drive on computers accessible only to CASD personnel. The video recordings will be used for analysis of the tester's reliability in administering measures included in the testing battery. The recordings may also be used for further analysis and/or interpretation of findings. The recordings may

also be used for educational purposes. Only CASD professional staff, study staff, and trainees will have access to this data. The video recordings will be stored on a secure drive on computers accessible only to CASD personnel. Identifiers will only be kept as far as the study remains op en and is under IRB oversight. Once the study is complete and IRB oversight is finished, all identifiers will be destroyed.

Brain imaging data files are stored on a server in Georgetown PD Vaidya's laboratory at GU without identifying information, using unique identifiers. The server is password protected, and the imaging data files are accessible only to PD Vaidya and Co-I You. Any paper forms of study record materials will be stored in locked filing cabinets in Vaidya's laboratory at GU.

**Certificate of Confidentiality**

To further protect study participants, a Certificate of Confidentiality has been obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding; whether at the federal, state, or local level. The certificate protects researchers and institutions from being compelled to disclose information that would identify research participants,

### 10.5 Study Support and Conflicts of Interest

Study support is provided by The Clinical and Translational Science Institute (CTSI) at Children's National. All key study personnel will follow the Human Research Protections Program Investigator, Study Staff, and Family Member Conflicts of Interest (COI) Policy.

## Section 11: Data Handling and Record Keeping

### 11.1 Data Management Responsibilities

Study data will be collected by study staff. The PIs will have continuous oversight over study management, education of team members and intra-study communications. The PIs will be in constant contact with all study staff members throughout the study, and will have regular meetings to discuss issues, questions, and next steps. The PIs and research staff will be available via email and/or phone throughout the course of the study to ensure proper implementation of study, provide guidance and facilitate communication.

### 11.2 Data Capture Methods

Data from behavioral assessments and learnings tasks will be facilitated by REDCap®, a password protected, secure, Health Insurance Portability and Accountability Act (HIPAA) compliant, web-based electronic database with a built-in audit trail.

All study participants will be assigned a unique ID number upon entering the study and their responses to surveys and tasks will be de-identified with only the ID number attached to it to increase confidentiality and security. De-identified survey data will be entered directly from the source documents into REDCap® within 10 days of collection. Only study staff will have access to a secure spreadsheet that connects participant identifying information (e.g., name, email) with their study ID in order to maintain contact with study participants.

Data collection is the responsibility of the research study staff. The PD is responsible for ensuring the accuracy, completeness, legibility, timeliness and completeness of the data reported. Only Institutional Review Board (IRB) approved research team members who have current HIPAA and Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) and human subject's protection training will be authorized to extract data from source documents and enter it into REDCap®. Online data will be collected using the secure survey option in REDcap and the Gorilla and Inquisit platforms.

### 11.3 Study Record Retention Policy

We will retain study data for 5 years after the completion of the study, and we will then delete the redcap database and all files pertaining to study records.

## Section 12: Publication Policy

As Project Directors of this grant application and clinical trial, we will ensure that the proposed clinical trial is registered at, and that summary results are submitted to ClinicalTrials.gov for public posting to support the NIH mission to advance the translation of research results into knowledge, products, and procedures that improve human health. Dr. Kenworthy and Dr. Verbalis at CNH will be responsible for all Clinical trials.gov related tasks. Specifically, we will

- Ensure that this trial is registered and results information is submitted to Clinical Trials.gov according to NIH policy for the specific timelines outlined below:
    - The trial will be registered not more than 21 calendar dates after the enrollment of the first participant
    - Results information will be submitted no more than one year after the trial's primary completion date
    - Registration information will be updated no less than once every 6 months
    - If recruitment status for the study changes, the registration will be updated within 30 days
    - If the trial is complete, registration will be updated within 30 days.
- Include a specific statement relating to posting of clinical trials information at ClinicalTrials.gov in informed consent and assent documents
    - The Children's National IRB has specific template language explaining that the study will be posted on clinicaltrials.gov that investigators are required to include in the consent document for the trial (e.g., "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.")

As Project Directors, we will work closely with the Children's National ClinicalTrials.gov liaison within the Compliance Department of Children's Research Institute to conduct the proposed project in accordance with Children's National's internal policy to ensure that clinical trials registration and results reporting occur in compliance with policy requirements. Children's National is committed to transparency and research integrity in its research activities. Children's National requires that all investigators comply with the requirements of Health and Human Services (HHS) regulations (42 CFR 11) (FDAAA 801), "Clinical Trials Registration and Results Information Submission," and the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information." Children's National has an organizational account to register clinical trials on Clinical Trials.gov. Children's National reserves the right to impose discipline or sanctions for non-compliance. An investigator that does not respond to the ClinicalTrials.gov Navigator's request for compliance within 10 business days may incur one or more consequences. Consequences may include limitations on the ability to conduct research. Determinations regarding non-compliance with Clinical Trials.gov requirements will be made jointly by the Children's National Offices of Corporate Compliance and Regulatory Affairs.

In partnership with the Clinical and Translational Science Institute at Children's National (CTSI-CN), Children's National offers the following support services to help investigators comply with these guidelines:

- ClinicalTrials.gov Liaison: Providing investigator consultations and support for study registration, update of study records and data reporting into ClinicalTrials.gov within the federally required timeframes.
- Biostatistician Support for Data Analysis and Result Reporting: the CTSI-CN has a Biostatistics, Epidemiology and Research Design (BERD) module that provides statistical consultation, analysis and proposal development to investigators. Consulting services include biostatistical and epidemiologic consultative services in study design, statistical analysis, data management, and data dissemination.

As Project Directors, we will work closely with Children's Research Institute to register this trial and submit summary results to the website in a timely manner, in keeping within the required timeframes. Once data collection is complete, we will work with our statistician to prepare and submit trial results no later than one year after the primary completion date.

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